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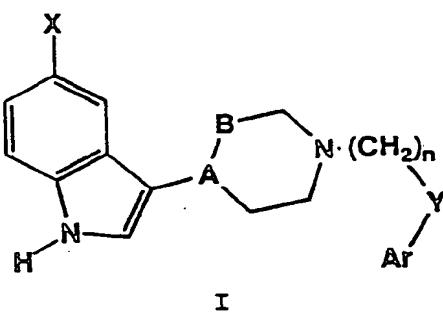
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(54) 3-(1,2,3,6-tetrahydro-(1-alkylenearyl)-4-pyridinyl)- and
3-(1-alkylenearyl)-4-piperidinyl-1h-indoles: new 5-HT_{1F} agonists

(57) This invention provides novel 5-HT_{1F} agonists
of formula I which are useful for the treatment of mi-
graine and associated disorders.



I

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Description

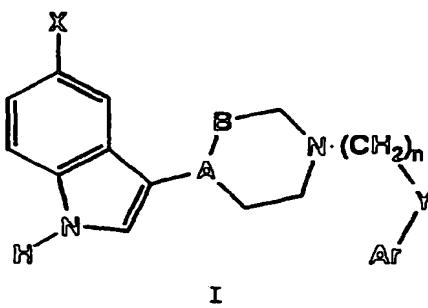
Theories regarding the pathophysiology of migraine have been dominated since 1938 by the work of Graham and Wolff (*Arch. Neurol. Psychiatry*, **39**, 737-63 (1938)). They proposed that the cause of migraine headache was vasodilation of extracranial vessels. This view was supported by knowledge that ergot alkaloids and sumatriptan, a hydrophilic 5-HT₁ agonist which does not cross the blood-brain barrier, contract cephalic vascular smooth muscle and are effective in the treatment of migraine. (Humphrey, et al., *Ann. NY Acad. Sci.*, **600**, 587-600 (1990)). Recent work by Moskowitz has shown, however, that the occurrence of migraine headaches is independent of changes in vessel diameter (*Cephalalgia*, **12**, 5-7, (1992)).

Moskowitz has proposed that currently unknown triggers for pain stimulate trigeminal ganglia which innervate vasculature within the cephalic tissue, giving rise to release of vasoactive neuropeptides from axons on the vasculature. These released neuropeptides then activate a series of events, a consequence of which is pain. This neurogenic inflammation is blocked by sumatriptan and ergot alkaloids by mechanisms involving 5-HT receptors, believed to be closely related to the 5-HT_{1D} subtype, located on the trigeminovascular fibers (*Neurology*, **43**(suppl. 3), S16-S20 (1993)).

Serotonin (5-HT) exhibits diverse physiological activity mediated by at least four receptor classes, the most heterogeneous of which appears to be 5-HT₁. A human gene which expresses a fifth 5-HT₁ subtype, named 5-HT_{1F}, was isolated by Kao and coworkers (*Proc. Natl. Acad. Sci. USA*, **90**, 408-412 (1993)). This 5-HT_{1F} receptor exhibits a pharmacological profile distinct from any serotonergic receptor yet described. The high affinity of sumatriptan at this subtype, $K_i=23$ nM, suggests a role of the 5-HT_{1F} receptor in migraine.

This invention provides novel 5-HT_{1F} agonists which inhibit peptide extravasation due to stimulation of the trigeminal ganglia, and are therefore useful for the treatment of migraine and associated disorders.

The present invention provides novel optionally substituted 3-<1,2,3,6-tetrahydro-*<1-alkylenearyl>-4-pyridinyl>-1H-indoles and 3-<1-alkylenearyl>-4-piperidinyl>-1H-indoles of Formula I:*



in which

A-B is -CH-CH₂- or -C=CH-;

X is H, halo, C₁-C₄ alkoxy, C₁-C₄ alkylthio, C₁-C₄ alkyl, benzyloxy, hydroxy or carboxamido;

Y is O, S or a bond;

n is 1-4;

Ar is 1-naphthyl, 2-naphthyl, phenyl or phenyl monosubstituted with a substituent selected from the group consisting of halo, C₁-C₄ alkoxy, C₁-C₄ alkylthio, C₁-C₄ alkyl, benzyloxy, hydroxy or trifluoromethyl; and

pharmaceutically acceptable acid addition salts and hydrates thereof providing that:

a) when Ar is phenyl and Y is a bond, X is other than halo; and

b) when A-B is -C=CH-:

i) X is not H or methoxy when Ar is phenyl and Y is a bond;

ii) X is not H when Ar is 4-chlorophenyl, n is 1 and Y is a bond;

iii) X is not hydroxy or benzyloxy when Ar is phenyl, n is 1 and Y is a bond.

This invention also provides a pharmaceutical formulation which comprises, in association with a pharmaceutically acceptable carrier, diluent or excipient, a compound of Formula I.

A further embodiment of this invention is a method for increasing activation of the 5-HT_{1F} receptor for treating a

variety of disorders which have been linked to decreased neurotransmission of serotonin in mammals. Included among these disorders are depression, migraine pain, bulimia, premenstrual syndrome or late luteal phase syndrome, alcoholism, tobacco abuse, panic disorder, anxiety, post-traumatic syndrome, memory loss, dementia of aging, social phobia, attention deficit hyperactivity disorder, disruptive behavior disorders, impulse control disorders, borderline personality disorder, obsessive compulsive disorder, chronic fatigue syndrome, premature ejaculation, erectile difficulty, anorexia nervosa, disorders of sleep, autism, mutism or trichotillomania. Any of these methods employ a compound of Formula I.

The general chemical terms used in the formulae above have their usual meanings. For example, the terms C₁-C₄ alkyl, C₁-C₄ alkoxy and C₁-C₄ alkylthio, include such groups as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl and s-butyl. The term halo includes fluoro, chloro, bromo and iodo.

While all of the compounds of this invention are useful as 5-HT_{1F} agonists, certain of the compounds are preferred. It is preferred that n is 2-4, Y is a bond, and that Ar is phenyl or phenyl monosubstituted with a substituent selected from the group consisting of halo, C₁-C₄ alkoxy, C₁-C₄ alkylthio, C₁-C₄ alkyl, hydroxy or trifluoromethyl.

It is more preferred that n is 2-4, Y is a bond, X is H, halo, carboxamido, methoxy, benzyloxy or hydroxy, and that Ar is phenyl or phenyl monosubstituted with a substituent selected from the group consisting of halo, C₁-C₄ alkoxy, C₁-C₄ alkyl, or trifluoromethyl.

It is most preferred that n is 2 or 4, X is H, halo, carboxamido, benzyloxy or hydroxy, Y is a bond and Ar is phenyl or phenyl monosubstituted in the 3-position with a substituent selected from the group consisting of fluoro, chloro, methoxy, methyl or trifluoromethyl.

The compounds of this invention are useful in a method for increasing activation of the 5-HT_{1F} receptor for treating a variety of disorders which have been linked to decreased neurotransmission of serotonin in mammals. It is preferred that the mammal to be treated by the administration of compounds of this invention is human.

Since the compounds of this invention are amines, they are basic in nature and accordingly react with any of a number of inorganic and organic acids to form pharmaceutically acceptable acid addition salts. Since some of the free amines of the compounds of this invention are typically oils at room temperature, it is preferable to convert the free amines to their pharmaceutically acceptable acid addition salts for ease of handling and administration, since the latter are routinely solid at room temperature. Acids commonly employed to form such salts are inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, phosphoric acid, and the like, and organic acids, such as p-toluene-sulfonic acid, methanesulfonic acid, oxalic acid, p-bromo-phenylsulfonic acid, carbonic acid, succinic acid, citric acid, benzoic acid, acetic acid and the like. Examples of such pharmaceutically acceptable salts thus are the sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, propionate, decanoate, caprylate, acrylate, formate, isobutyrate, caproate, heptanoate, propiolate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, butyne-1,4-dioate, hexyne-1,6-dioate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, phthalate, sulfonate, xylenesulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate, b-hydroxybutyrate, glycolate, tartrate, methanesulfonate, propanesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, mandelate and the like. Preferred pharmaceutically acceptable salts are those formed with hydrochloric acid or oxalic acid.

The following group is illustrative of compounds contemplated within the scope of this invention:

3-<1-<2-phenyl>ethyl>-4-piperidinyl>-1H-indole hydrochloride
 5-methoxy-3-<1-<3-phenyl>propyl>-4-piperidinyl>-1H-indole hydrochloride
 5-bromo-3-<1-<2-<1-naphthyl>ethyl>-4-piperidinyl>-1H-indole oxalate
 5-chloro-3-<1-<3-<4-trifluoromethylphenyl>propyl>-4-piperidinyl>-1H-indole mandelate
 5-carboxamido-3-<1-<2-phenyl>ethyl>-4-piperidinyl>-1H-indole hydrobromide
 5-chloro-3-<1-<2-<2-naphthyl>ethyl>-4-piperidinyl>-1H-indole p-toluenesulfonate
 5-hydroxy-3-<1-<2-<3-thiomethylphenyl>ethyl>-4-piperidinyl>-1H-indole
 5-propyl-3-<1-<3-<4-methoxyphenyl>ethyl>-4-piperidinyl>-1H-indole
 5-iodo-3-<1-<4-<2-chlorophenyl>butyl>-4-piperidinyl>-1H-indole benzoate
 5-butoxy-3-<1-<2-<4-ethoxyphenyl>ethyl>-4-piperidinyl>-1H-indole methanesulfonate
 5-fluoro-3-<1-<4-thioethylphenyl>methyl>-4-piperidinyl>-1H-indole
 5-isobutyl-3-<1-<3-<2-trifluoromethylphenyl>propyl>-4-piperidinyl>-1H-indole
 5-butyl-3-<1-<2-<3-fluorophenyl>ethyl>-4-piperidinyl>-1H-indole hydrochloride
 5-ethyl-3-<1-<1,2,3,6-tetrahydro-<2-<4-isopropylphenyl>ethyl>-4-piperidinyl>>-1H-indole
 5-methyl-3-<1-<1,2,3,6-tetrahydro-<2-naphthyl>methyl>-4-piperidinyl>>-1H-indole
 5-isopropoxy-3-<1-<1,2,3,6-tetrahydro-<2-<2-methylphenyl>ethyl>-4-piperidinyl>>-1H-indole hydrobromide
 5-isopropyl-3-<1-<1,2,3,6-tetrahydro-<4-benzoyloxyphenyl>ethyl>-4-piperidinyl>>-1H-indole maleate
 5-ethoxy-3-<1-<1,2,3,6-tetrahydro-<2-<4-isopropylphenyl>ethyl>-4-piperidinyl>>-1H-indole

5-(sec-butoxy)-3-<1-<1,2,3,6-tetrahydro-<2-<3-bromophenyl>ethyl>-4-piperidinyl>>-1H-indole
5-iodo-3-<1-<1,2,3,6-tetrahydro-<4-<2-chlorophenyl>butyl>-4-piperidinyl>-1H-indole benzoate

5 The compounds of this invention are prepared by methods well known to one of ordinary skill in the art. A majority of the starting indoles are commercially available, however, they may be prepared by the Fischer indole synthesis (Robinson, *The Fischer Indole Synthesis*, Wiley, New York, 1983).

The indoles are condensed with 4-piperidone-HCl-H₂O or, when commercially available, an appropriately N-substituted 4-piperidone, in the presence of a suitable base to give the corresponding 3-(1,2,3,6-tetrahydro-4-pyridinyl)-1H-indoles as illustrated in the following scheme.

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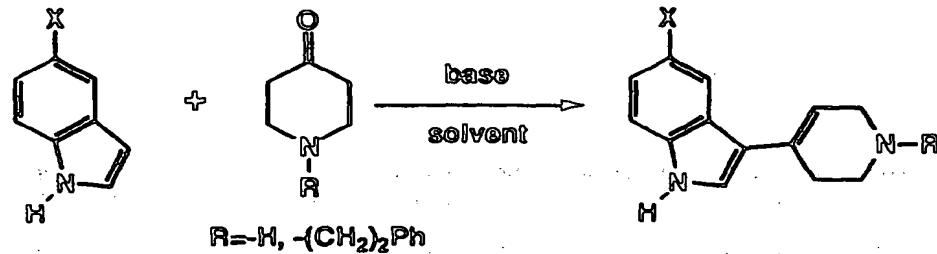
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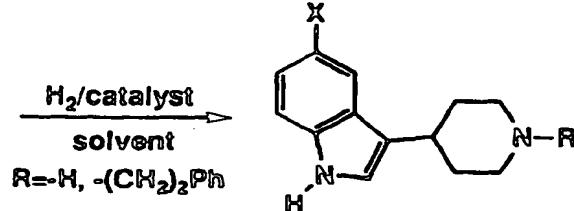
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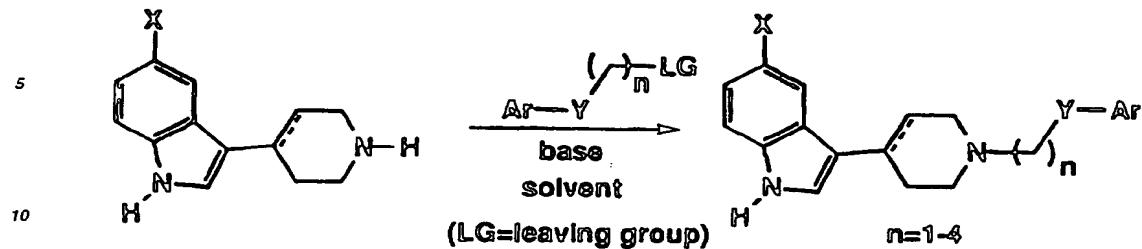
The reaction is performed by first dissolving an excess of the base, typically sodium or potassium hydroxide, in a lower alkanol, typically methanol or ethanol. The indole and two equivalents of the 4-piperidone are then added and the reaction refluxed for 8-72 hours. The resulting 3-(1,2,3,6-tetrahydro-4-pyridinyl)-1H-indoles may be isolated from the reaction mixture by the addition of water. Compounds which precipitate may be isolated directly by filtration while others may be extracted with a water immiscible solvent such as ethyl acetate or dichloromethane. The compounds recovered may be used directly in subsequent steps or first purified by silica gel chromatography or recrystallization from a suitable solvent.

The 3-(1,2,5,6-tetrahydro-4-pyridinyl)-1H-indoles may next be hydrogenated to give the corresponding 3-(piperidin-4-yl)-1H-indoles as shown below.



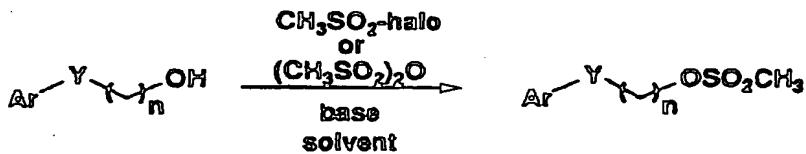
The catalyst may be a precious metal catalyst such as platinum oxide, or palladium or platinum on a suitable support such as carbon. When X is a functional group that is labile to hydrogenolysis, such as halo or benzyloxy, a deactivated catalyst such as sulfided platinum on carbon or a mixed catalyst system of sulfided platinum on carbon with platinum oxide may be used to prevent hydrogenolysis. The solvent may consist of a lower alkanol, such as methanol or ethanol, tetrahydrofuran or a mixed solvent system of tetrahydrofuran and ethyl acetate. The hydrogenation may be performed at an initial hydrogen pressure of 20-80 p.s.i., preferably from 50-60 p.s.i., at 0-60°C, preferably at ambient temperature to 40°C, for 1 hour to 3 days. Additional charges of hydrogen may be required to drive the reaction to completion depending on the specific substrate. The 3-(piperidin-4-yl)-1H-indoles prepared in this manner are isolated by removal of the catalyst by filtration followed by concentration of the reaction solvent under reduced pressure. The product recovered may be used directly in a subsequent step or further purified by chromatography or recrystallization from a suitable solvent.

When R is H, either the 3-(1,2,3,6-tetrahydro-4-pyridinyl)-1H-indoles or the 3-(piperidin-4-yl)-1H-indoles prepared as described above are suitable substrates for N-alkylation with an appropriate alkylating agent as described below.



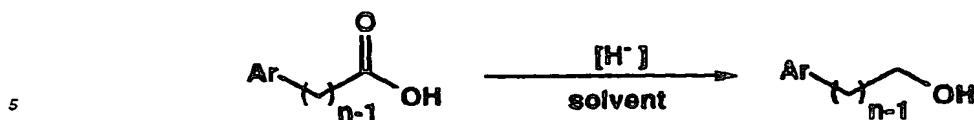
The starting indole and the base are combined in the reaction solvent followed by the addition of the alkylating agent. The reaction solvent may be any non-reactive solvent typically used for alkylations of this type such as acetonitrile, dimethylformamide or N-methyl-2-pyrrolidinone, limited by the solubility of the substrates and a sufficiently high boiling point. The base must be sufficiently basic to neutralize the acid generated during the progress of the reaction but not so basic as to deprotonate other sites in the substrate giving rise to other products. Additionally, the base must not compete to any great extent with the substrate for the alkylating agent and must have sufficient solubility in the reaction solvent. Bases typically used for these reactions are sodium carbonate or potassium carbonate. The reaction mixture is typically stirred at 80 to 140°C, preferably at about 100°C, for 8 hours to 3 days. The alkylated products are isolated by concentration of the reaction mixture under reduced pressure followed by partitioning of the resultant residue between water and a suitable organic solvent such as ethyl acetate, diethyl ether, dichloromethane, ethylene chloride, chloroform or carbon tetrachloride. The isolated product may be purified by chromatography, crystallization from a suitable solvent, salt formation or a combination of these techniques.

The leaving group (LG) of the alkylating agents may be chloro, bromo, iodo, methanesulfonyloxy, trifluoromethanesulfonyloxy, 2,2,2-trifluoroethanesulfonyloxy, benzenesulfonyloxy, p-bromobenzenesulfonyloxy, p-nitrobenzenesulfonyloxy or p-toluenesulfonyloxy, all of which are useful for the preparation of compounds of this invention. The specific alkylating agent employed is determined by its commercial availability or a convenient synthesis from commercially available starting materials. The preferred alkylating agents for synthesis of compounds of this invention are those where the leaving group is chloro, bromo or methanesulfonyloxy. Alkylating agents where the leaving group is chloro, if not commercially available, are prepared from the corresponding alcohol by standard methods, preferably by treating the alcohol with neat thionyl chloride at ambient temperature. Alkylating agents where the leaving group is methanesulfonyloxy are prepared from the corresponding alcohols as described below.



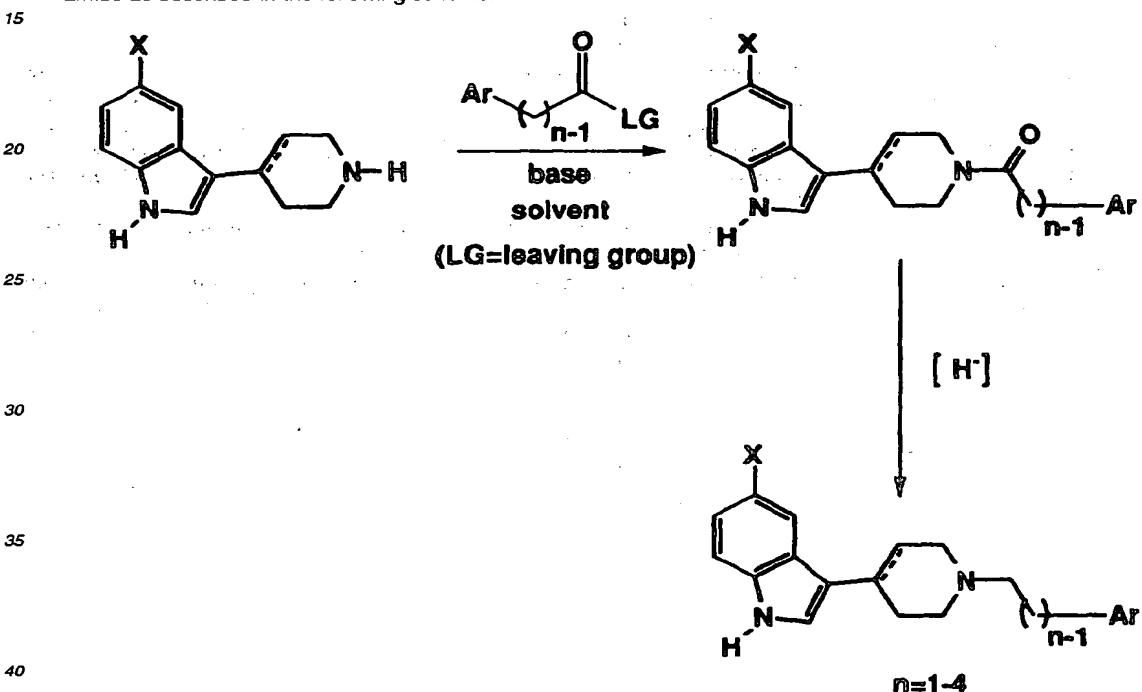
The alcohol is dissolved in a suitable anhydrous solvent such as tetrahydrofuran, diethyl ether, p-dioxane or acetonitrile which contains the base. The base must be sufficiently basic to neutralize the acid generated during the progress of the reaction but not so basic as to deprotonate other sites in the substrate giving rise to other products. Additionally, the base must not compete to any great extent with the substrate for the sulfonating reagent and must have sufficient solubility in the reaction solvent. Bases typically used in these reactions are tertiary amines such as pyridine, triethylamine or N-methylmorpholine. To the reaction mixture is then added the sulfonating reagent with cooling. The sulfonating reagent may be a methanesulfonyl halide such as the fluoride or chloride, or methanesulfonic anhydride. The reaction mixture is allowed to react from 1 hour to 24 hours at ambient temperature. The product is isolated by concentrating the reaction mixture under reduced pressure followed by partitioning the residue between water and an appropriate organic solvent such as dichloromethane, ethylene chloride, chloroform or carbon tetrachloride. The isolated product is used directly in the alkylation step.

The starting alcohols required for the synthesis of compounds of this invention are either commercially available or may be prepared by employing well established synthetic methodology. A general scheme for the synthesis of a number of the required alcohols is described below.



An appropriate carboxylic acid is reduced to the corresponding alcohol in diethyl ether or, preferably, tetrahydrofuran. The solution is added to a suspension of an appropriate hydride reducing agent, preferably lithium aluminum hydride, in the same solvent at reduced temperature, typically about 0°C. Once the addition is complete the mixture is allowed to warm to ambient and is stirred at ambient to reflux until the reduction is complete. The alcohol recovered may typically be used without further purification.

10 Compounds of this invention may alternatively be prepared by N-acylation of the 3-(1,2,3,6-tetrahydro-4-pyridinyl)-1H-indoles or the 3-(piperidin-4-yl)-1H-indoles with an appropriate acylating agent followed by reduction of the resulting amide as described in the following scheme.



The 3-(1,2,3,6-tetrahydro-4-pyridinyl)-1H-indoles or the 3-(piperidin-4-yl)-1H-indoles are acylated in a suitable solvent such as dimethylformamide or N-methyl-2-pyrrolidinone with an appropriate acyl halide, preferably an acyl chloride, or an activated ester well known in the synthesis of peptides such as the esters of pentafluorophenol or 2,4,5-trichlorophenol. When an acyl halide is used a suitable base, preferably potassium carbonate, is also required in the reaction mixture to neutralize the acid that is formed as the reaction progresses. The reactions are typically performed at ambient to 80°C for from one hour to three days. The amide prepared in this reaction is then reduced to a compound of this invention with a suitable hydride reducing agent, such as lithium aluminum hydride, aluminum hydride, sodium aluminum hydride, borane tetrahydrofuran complex or borane dimethylsulfide complex, in an anhydrous ethereal solvent such as tetrahydrofuran or diethyl ether. The reaction is typically run at reflux for from 1 to 24 hours. The desired products are recovered by decomposition of the intermediate complexes by the addition of water followed by extraction into a suitable solvent such as ethyl acetate, diethyl ether or dichloromethane.

When a hydroxy substituted compound of this invention is desired, it is easily prepared by catalytic O-debenzylation of the corresponding benzyloxy compound. Furthermore, compounds of this invention which contain a benzyl group on a nitrogen atom of the pyrazolyl or pyrrolyl moiety may be N-debenzylated to give other compounds of this invention. These hydrogenolyses may be performed by dissolution of the substrate in a lower alkanol, such as methanol or ethanol, tetrahydrofuran or a mixed solvent system of tetrahydrofuran and ethyl acetate. The hydrogenation may be

performed at an initial hydrogen pressure of 20-80 p.s.i., preferably from 50-60 p.s.i., at 0-60°C, preferably at ambient temperature to 40°C, for 1 hour to 3 days. Additional charges of hydrogen may be required to drive the reaction to completion depending on the specific substrate. Compounds prepared in this manner are isolated by removal of the catalyst by filtration followed by concentration of the reaction solvent under reduced pressure. The product recovered
5 may be purified by chromatography or recrystallization from a suitable solvent if necessary.

It is evident to the skilled artisan that the conditions for hydrogenolysis of an N- or O-benzyl group are identical to those required for the reduction of the 4,5-double bond of the tetrahydropyridines described *supra*. The hydrogenolysis and double-bond reduction steps, therefore, may be combined if desired. Additionally, the skilled artisan would understand that, where substituents allow, the order of N-alkylation and double-bond reduction is not important.

10 The following preparations and examples further illustrate the synthesis of the compounds of this invention and are not intended to limit the scope of the invention in any way. The compounds described below were identified by various standard analytical techniques as stated in the individual preparations and examples.

All of the 3-[1,2,3,6-tetrahydro-4-pyridinyl]-1H-indoles useful as intermediates for compounds of this invention may be prepared as described in the following procedure.
15

PREPARATION I

5-bromo-3-<1,2,3,6-tetrahydro-4-pyridinyl>-1H-indole

20 To a solution of 4.29 gm (77 mMol) potassium hydroxide in 50 mL methanol were added 5.0 gm (26 mMol) 5-bromoindole and 7.84 gm (51 mMol) 4-piperidone-HCl·H₂O and the reaction mixture was stirred for 18 hours at reflux under a nitrogen atmosphere. The reaction mixture was cooled to ambient temperature, diluted with 500 mL water and the mixture extracted well with dichloromethane. The combined organic extracts were washed with water followed by saturated aqueous sodium chloride and dried over sodium sulfate. The remaining organics were concentrated under reduced pressure to give 6.23 gm (86.5%) of the title compound as a yellow oil. ¹H-NMR(DMSO-d₆): δ 8.00 (s, 1H); 7.40 (s, 1H); 7.30(d, 1H); 7.20 (d, 1H); 6.10 (s, 1H); 3.35 (br s, 2H); 2.85 (m, 2H); 2.35 (br s, 2H).

25 All of the 3-[piperidin-4-yl]-1H-indoles useful as intermediates for compounds of this invention may be prepared as described in the following procedure.

30 PREPARATION II

5-bromo-3-[piperidin-4-yl]-1H-indole

35 To a solution of 13.61 gm (49 mMol) 5-bromo-3-<1,2,3,6-tetrahydro-4-pyridinyl>-1H-indole in 75 mL 2:1 tetrahydrofuran:ethyl acetate were added 8.0 gm 3% sulfided platinum on carbon and 4.0 gm platinum oxide. The reaction mixture was hydrogenated with an initial hydrogen pressure of 60 p.s.i. at 40°C for 18 hours and then at ambient temperature for 30 hours. The reaction mixture was filtered and the filtrate concentrated under reduced pressure to give 10.33 gm (75.6%) of the title compound as a light yellow solid.
MS(m/e): 278(M⁺).

40 ¹H-NMR (DMSO-d₆): δ 10.6 (s, 1H); 7.2 (d, 1H); 7.05 (s, 2H); 6.7 (d, 1H); 3.15 (s, 1H); 3.05 (s, 1H); 2.8 (m, 3H), 1.95 (s, 1H); 1.85 (s, 1H); 1.6 (m, 2H).

PREPARATION III.

45 5-carboxamidoindole

To a solution of 8.06 gm (50 mMol) indole-5-carboxylic acid in 150 mL dimethylformamide were added 8.11 gm (50 mMol) carbonyldiimidazole and the reaction mixture stirred at ambient temperature for 3 hours. The reaction mixture was then added dropwise to 150 mL concentrated ammonium hydroxide and the reaction mixture was stirred for 18 hours at ambient temperature. The reaction mixture was concentrated under reduced pressure to give a viscous oil which was subjected to silica gel chromatography, eluting with a gradient of dichloromethane containing 0-10% methanol. Fractions shown to contain product were combined and concentrated under reduced pressure to give the title compound as an oil which crystallizes upon standing.
1H-NMR(CDCl₃): δ 8.18(s, 1H); 7.74 (d, 1H); 7.45 (d, 1H); 7.35 (s, 1H); 6.65 (s, 1H).

55 The following procedure is typical for the preparation of most of the aralkanols useful for preparation of compounds of the present invention.

PREPARATION IV

2-(3-fluorophenyl)ethanol

5 To a suspension of 3.07 gm (81 mMol) lithium aluminum hydride in 115 mL diethyl ether at 0°C were added dropwise a solution of 7.0 gm (45 mMol) 3-fluorophenylacetic acid in 26 mL tetrahydrofuran dropwise. The reaction was allowed to warm to ambient and then stirred 18 hours. The reaction mixture was quenched by the addition of 3.0 mL 2 N NaOH dropwise with cooling. To this mixture was then added 9.0 mL water and the resulting suspension stirred for 1 hour at ambient. The suspension was filtered and the filter cake rinsed well with diethyl ether. The filtrate was concentrated under reduced pressure to give 6.26 gm (100%) of the title compound as a clear oil. The product was used without further purification.

10 The aralkanols were converted to their corresponding mesylates by the method described below.

PREPARATION V

15 1-(2-methanesulfonyloxyethyl)-2-chlorobenzene

To a solution of 5.26 mL (40 mMol) 2-(2-chlorophenyl)ethanol and 8.36 mL (60 mMol) triethylamine in 100 mL tetrahydrofuran were added dropwise 3.25 mL (42 mMol) methanesulfonyl chloride with cooling. The reaction mixture 20 was stirred 4 hours at ambient and was then concentrated under reduced pressure. The residue was partitioned between dichloromethane and water. The organic phase was separated and washed sequentially with water and saturated aqueous sodium chloride. The remaining organics were dried over sodium sulfate and concentrated under reduced pressure to give 9.22 gm (98.3%) of the title compound as a yellow oil. The product was used without further purification.

25 EXAMPLE 1

3-<1-<2-<2-fluorophenyl>ethyl>-4-piperidinyl>-1H-indole hydrochloride

To a solution of 2.10 gm (10.0 mMol) 3-(4-piperidinyl)-1H-indole in 40 mL dimethylformamide were added 2.65 gm 30 sodium carbonate followed by the dropwise addition of a solution of 2.18 gm (10.0 mMol) 1-(2-methanesulfonyloxyethyl)-2-fluorobenzene in 8.0 mL dimethylformamide. The reaction mixture was stirred at 100°C for 18 hours under a nitrogen atmosphere. The reaction mixture was then cooled to ambient and the solvent removed under reduced pressure. The residue was partitioned between water and dichloromethane. The organic phase was separated and washed twice with water and once with saturated aqueous sodium chloride. The remaining organics were dried over sodium 35 sulfate and concentrated under reduced pressure to give 3.62 gm of a yellow oil. The oil was purified by flash chromatography, eluting with a gradient system consisting of dichloromethane containing 0-5% methanol. Fractions shown to contain product were combined and concentrated under reduced pressure to give a yellow oil. The hydrochloride salt was formed to give 1.53 gm (42.7%) of the title compound as yellow crystals from methanol, m.p.>250°C (dec). MS(m/e): 322(M⁺)

40 Calculated for C₂₁H₂₃N₂F·HCl: Theory: C, 70.28; H, 6.74; N, 7.81. Found: C, 70.42; H, 6.82; N, 7.93.

The compounds of Examples 2-17 were prepared employing the method described in detail in Example 1.

EXAMPLE 2

45 3-<1-<2-<3-fluorophenyl>ethyl>-4-piperidinyl>-1H-indole hydrochloride

Using 1.0 gm (5.0 mMol) 3-(4-piperidinyl)-1H-indole and 1.09 gm (5.0 mMol) 1-(2-methanesulfonyloxyethyl)-3-fluorobenzene, 0.87 gm (48.5%) of the title compound were recovered from methanol as colorless crystals, m.p.=297°C.

50 MS(m/e): 322(M⁺)

Calculated for C₂₁H₂₃N₂F·HCl: Theory: C, 70.28; H, 6.74; N, 7.81. Found: C, 70.52; H, 6.72; N, 7.77.

EXAMPLE 3

55 3-<1-<2-<4-fluorophenyl>ethyl>-4-piperidinyl>-1H-indole hydrochloride

Using 1.0 gm (5.0 mMol) 3-(4-piperidinyl)-1H-indole and 1.09 gm (5.0 mMol) 1-(2-methanesulfonyloxyethyl)-4-fluorobenzene, 0.87 gm (48.5%) of the title compound were recovered from methanol as pink crystals, m.p.>250°C.

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MS(m/e): 322(M⁺)

Calculated for C₂₁H₂₃N₂F·HCl: Theory: C, 70.28; H, 6.74; N, 7.81. Found: C, 70.07; H, 6.92; N, 7.79.

EXAMPLE 4

5

5-methoxy-3-<1-<2-<4-fluorophenyl>ethyl>-4-piperidinyl>-1H-indole hydrochloride

Using 2.0 gm (8.7 mMol) 5-methoxy-3-(4-piperidinyl)-1H-indole and 1.90 gm (8.7 mMol) 1-(2-methanesulfonyloxyethyl)-4-fluorobenzene, 1.76 gm (52.1%) of the title compound were recovered from as brown crystals, m.p.=215°C.

10

MS(m/e): 352 (M⁺)

Calculated for C₂₁H₂₅N₂OF·HCl: Theory: C, 67.94; H, 6.74; N, 7.20. Found: C, 67.89; H, 6.80; N, 7.29.

EXAMPLE 5

15

3-<1-<2-<2-chlorophenyl>ethyl>-4-piperidinyl>-1H-indole hydrochloride

Using 1.0 gm (5.0 mMol) 3-(4-piperidinyl)-1H-indole and 1.17 gm (5.0 mMol) 1-(2-methanesulfonyloxyethyl)-2-chlorobenzene, 1.00 gm (53.3%) of the title compound were recovered from methanol as light pink crystals, m.p.>250°C.

20

MS(m/e): 338(M⁺)

Calculated for C₂₁H₂₃N₂Cl·HCl: Theory: C, 67.20; H, 6.44; N, 7.46. Found: C, 66.96; H, 6.46; N, 7.42.

EXAMPLE 6

25

3-<1-<2-<3-chlorophenyl>ethyl>-4-piperidinyl>-1H-indole hydrochloride

Using 1.0 gm (5.0 mmol) 3-(4-piperidinyl)-1H-indole and 1.17 gm (5.0 mMol) 1-(2-methanesulfonyloxyethyl)-3-chlorobenzene, 0.76 gm (40.5%) of the title compound were recovered from methanol as pink crystals, m.p.>250°C.

MS(m/e): 338 (M⁺)

Calculated for C₂₁H₂₃N₂Cl·HCl: Theory: C, 67.20; H, 6.44; N, 7.46. Found: C, 66.92; H, 6.50; N, 7.60.

30

EXAMPLE 7

3-<1-<2-<4-bromophenyl>ethyl>-4-piperidinyl>-1H-indole hydrochloride

35

Using 1.0 gm (5.0 mMol) 3-(4-piperidinyl)-1H-indole and 1.40 gm (5.0 mMol) 1-(2-methanesulfonyloxyethyl)-4-bromobenzene, 1.10 gm (53.3%) of the title compound were recovered from methanol as off-white crystals, m.p.>250°C.

MS(m/e) : 382(M⁺)

Calculated for C₂₁H₂₃N₂Br·HCl: Theory: C, 60.08; H, 5.76; N, 6.67. Found: C, 59.80; H, 5.79; N, 6.64.

40

EXAMPLE 8

3-<1-<2-<2-methylphenyl>ethyl>-4-piperidinyl>-1H-indole hydrochloride

45

Using 1.0 gm (5.0 mMol) 3-(4-piperidinyl)-1H-indole and 1.07 gm (5.0 mMol) 1-(2-methanesulfonyloxyethyl)-2-methylbenzene, 0.63 gm (35.5%) of the title compound were recovered from methanol as tan crystals, m.p.>250°C.

MS(m/e): 318(M⁺)

Calculated for C₂₂H₂₆N₂·HCl: Theory: C, 74.45; H, 7.67; N, 7.89. Found: C, 74.18; H, 7.56; N, 7.77.

EXAMPLE 9

50

3-<1-<2-<3-methylphenyl>ethyl>-4-piperidinyl>-1H-indole hydrochloride

55

Using 1.0 gm (5.0 mMol) 3-(4-piperidinyl)-1H-indole and 1.07 gm (5.0 mMol) 1-(2-methanesulfonyloxyethyl)-3-methylbenzene, 0.76 gm (42.8%) of the title compound were recovered from methanol as off-white crystals, m.p. >250°C.

MS(m/e): 318(M⁺)

Calculated for C₂₂H₂₆N₂·HCl: Theory: C, 74.45; H, 7.67; N, 7.89. Found: C, 74.23; H, 7.72; N, 7.95.

EXAMPLE 10

3-<1-<2-<4-methylphenyl>ethyl>-4-piperidinyl>-1H-indole hydrochloride

5 Using 1.0 gm (5.0 mMol) 3-(4-piperidinyl)-1H-indole and 1.07 gm (5.0 mMol) 1-(2-methanesulfonyloxyethyl)-4-methylbenzene, 0.71 gm (40.0%) of the title compound were recovered from methanol as yellow crystals, m.p. >250°C.
 MS(m/e): 318(M⁺)
 Calculated for C₂₂H₂₆N₂·HCl: Theory: C, 74.45; H, 7.67; N, 7.89. Found: C, 74.51; H, 7.77; N, 7.88.

EXAMPLE 11

3-<1-<2-<2-methoxyphenyl>ethyl>-4-piperidinyl>-1H-indole hydrochloride

15 Using 1.0 gm (5.0 mMol) 3-(4-piperidinyl)-1H-indole and 1.15 gm (5.0 mMol) 1-(2-methanesulfonyloxyethyl)-2-methoxybenzene, 0.79 gm (42.6%) of the title compound were recovered from methanol as pink crystals, m.p. =290-292°C.
 MS(m/e): 334(M⁺)
 Calculated for C₂₂H₂₆N₂O·HCl: Theory: C, 71.24; H, 7.34; N, 7.55. Found: C, 71.26; H, 7.33; N, 7.66.

EXAMPLE 12

3-<1-<2-<3-methoxyphenyl>ethyl>-4-piperidinyl>-1H-indole hydrochloride

25 Using 1.0 gm (5.0 mMol) 3-(4-piperidinyl)-1H-indole and 1.15 gm (5.0 mMol) 1-(2-methanesulfonyloxyethyl)-3-methoxybenzene, 0.95 gm (51.2%) of the title compound were recovered from methanol as pink crystals, m.p. >250°C.
 MS(m/e): 334(M⁺)
 Calculated for C₂₂H₂₆N₂O·HCl: Theory: C, 71.24; H, 7.34; N, 7.55. Found: C, 71.15; H, 7.30; N, 7.48.

EXAMPLE 13

5-methoxy-3-<1-<2-<4-methoxyphenyl>ethyl>-4-piperidinyl>-1H-indole oxalate

35 Using 2.0 gm (8.7 mMol) 5-methoxy-3-(4-piperidinyl)-1H-indole and 2.0 gm (8.7 mMol) 1-(2-methanesulfonyloxyethyl)-4-methoxybenzene, 1.17 gm (29.6%) of the title compound were recovered from methanol as yellow crystals, m.p.=127°C (dec).
 MS(m/e): 364(M⁺)
 Calculated for C₂₃H₂₈N₂O₂·C₂H₂O₄: Theory: C, 66.06; H, 6.65; N, 6.16. Found: C, 65.77; H, 6.73; N, 6.42.

EXAMPLE 14

3-<1-<2-<4-ethoxyphenyl>ethyl>-4-piperidinyl>-1H-indole hydrochloride

45 Using 1.0 gm (5.0 mMol) 3-(4-piperidinyl)-1H-indole and 1.14 gm (5.0 mMol) 1-(2-methanesulfonyloxyethyl)-4-ethoxybenzene, 0.47 gm (24.4%) of the title compound were recovered from methanol as a colorless solid, m.p. =263°C.
 MS(m/e): 348(M⁺)
 Calculated for C₂₃H₂₈N₂O·HCl: Theory: C, 71.76; H, 7.59; N, 7.28. Found: C, 71.50; H, 7.58; N, 7.36.

EXAMPLE 15

3-<1-<2-<4-benzylxyphenyl>ethyl>-4-piperidinyl>-1H-indole

55 Using 2.0 gm (10.0 mMol) 3-(4-piperidinyl)-1H-indole and 3.19 gm (10.0 mMol) 1-(2-methanesulfonyloxyethyl)-4-benzylxybenzene, 1.09 gm (26.5%) of the title compound were recovered from methanol as colorless crystals, m.p.=180°C.
 MS(m/e): 410(M⁺)

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Calculated for C₂₈H₃₀N₂O: Theory: C, 81.91; H, 7.36; N, 6.82. Found: C, 81.53; H, 7.33; N, 7.04.

EXAMPLE 16

5 3-<1-<2-<2-trifluoromethylphenyl>ethyl>-4-piperidinyl>-1H-indole hydrochloride

Using 1.0 gm (5.0 mMol) 3-(4-piperidinyl)-1H-indole and 1.34 gm (5.0 mMol) 1-(2-methanesulfonyloxyethyl)-2-trifluoromethylbenzene, 0.89 gm (43.5%) of the title compound were recovered as a tan solid, m.p.=228-230°C.

MS(m/e): 372(M⁺)

10 Calculated for C₂₂H₂₃N₂F₃·HCl: Theory: C, 64.62; H, 5.92; N, 6.85. Found: C, 64.83; H, 6.17; N, 6.99.

EXAMPLE 17

15 3-<1-<2-<3-trifluoromethylphenyl>ethyl>-4-piperidinyl>-1H-indole

Using 1.0 gm (5.0 mMol) 3-(4-piperidinyl)-1H-indole and 1.34 gm (5.0 mMol) 1-(2-methanesulfonyloxyethyl)-3-trifluoromethylbenzene, 1.43 gm (76.8%) of the title compound were recovered from cyclohexane, m.p.=126°C.

MS(m/e): 372(M⁺)

20 Calculated for C₂₂H₂₃N₂F₃: Theory: C, 70.95; H, 6.23; N, 7.52. Found: C, 71.23; H, 6.34; N, 7.51.

EXAMPLE 18

5-fluoro-3-<1-<1,2,3,6-tetrahydro-<2-<phenyl>ethyl>-4-pyridinyl>>-1H-indole hydrochloride

25 To a solution of 11.0 gm (196 mMol) potassium hydroxide in 100 mL methanol are added 1.49 gm (11.0 mMol) 5-fluoro-1H-indole followed by 4.57 gm (22.5 mMol) N-phenethyl-4-piperidone. The reaction mixture is stirred at reflux under a nitrogen atmosphere for 18 hours. The reaction mixture is cooled to room temperature and then diluted with 200 mL water. The precipitate is filtered and dried overnight in a vacuum dessicator to give 4.44 gm of a crude orange solid. To a solution of 2.44 gm of this orange solid in methanol were added 1.0 equivalents 1.0 N HCl and the solution is concentrated to dryness under reduced pressure. The residue was crystallized from ethyl acetate/methanol to give 1.54 gm of the title compound as a light yellow solid, m.p.>220°C(dec).

MS(m/e): 320(M⁺)

Calculated for C₂₁H₂₁FN₂·HCl: Theory: C, 70.68; H, 6.21; N, 7.85. Found: C, 70.51; H, 6.18; N, 7.68.

The compounds of Examples 19-24 were prepared employing the method described in detail in Example 18.

35

EXAMPLE 19

3-<1-<1,2,3,6-tetrahydro-<2-<phenyl>ethyl>-4-pyridinyl>>-1H-indole

40 Using 3.6 gm (30.7 mMol) of 1H-indole and 12.5 gm (61.5 mMol) N-phenethyl-4-piperidone, 16.2 gm crude product were recovered as an orange solid. The solid was subjected to silica gel chromatography, eluting with a gradient consisting of dichloromethane containing 0-10% methanol. Fractions shown to contain product were combined and concentrated under reduced pressure to give 4.94 gm of the free base of the title compound which was then crystallized from ethyl acetate to give 3.61 gm (38.9%) of the title compound as yellow crystals, m.p.=199-201°C (dec).

45 Calculated for C₂₁H₂₂N₂: Theory: C, 83.40; H, 7.33; N, 9.26. Found: C, 83.59; H, 7.43; N, 9.38.

EXAMPLE 20

5-chloro-3-<1-<1,2,3,6-tetrahydro-<2-<phenyl>ethyl>-4-pyridinyl>>-1H-indole hydrochloride

50

Using 1.67 gm (11 mMol) 5-chloro-1H-indole and 4.57 gm (22.5 mMol) N-phenethyl-4-piperidone, 4.54 gm of crude product were recovered as an orange solid. 2.55 gm of this crude solid were converted to the hydrochloride salt to give 1.05 gm of the title compound as an off-white solid. m.p.>220°C (ethyl acetate/methanol)

MS(m/e): 336(M⁺)

55 Calculated for C₂₁H₂₁ClN₂·HCl: Theory: C, 67.56; H, 5.94; N, 7.50. Found: C, 67.61; H, 6.13; N, 7.39.

EXAMPLE 21

5-methoxy-3-<1-<1,2,3,6-tetrahydro-<2-<phenyl>ethyl>-4-pyridinyl>>-1H-indole hydrochloride

5 Using 1.62 gm (11 mMol) 5-methoxy-1H-indole and 4.57 gm (22.5 mMol) N-phenethyl-4-piperidone, 4.71 gm of crude product were recovered as a yellow solid. The solid was subjected to silica gel chromatography, eluting with dichloromethane containing 5% methanol. Fractions shown to contain product were combined and concentrated under reduced pressure to give 3.44 gm of the free base of the title compound. 2.00 gm of this solid were converted to the hydrochloride salt to give 1.26 gm of the title compound as light yellow crystals.

10 m.p.>220°C (dec)(ethyl acetate/methanol)

MS(m/e): 332(M⁺)

Calculated for C₂₂H₂₄N₂O·HCl: Theory: C, 71.63; H, 6.83; N, 7.59. Found: C, 71.88; H, 6.89; N, 7.60.

EXAMPLE 22

15

5-benzyloxy-3-<1-<1,2,3,6-tetrahydro-<2-<phenyl>ethyl>-4-pyridinyl>>-1H-indole hydrochloride

Using 2.46 gm (11 mMol) 5-benzyloxy-1H-indole and 4.57 gm (22.5 mMol) N-phenethyl-4-piperidone, 9.92 gm of crude product were recovered as an orange solid. The solid was subjected to silica gel chromatography, eluting with dichloromethane containing 5% methanol and a trace of ammonium hydroxide. Fractions shown to contain product were combined and concentrated under reduced pressure to give 3.87 gm of the free base of the title compound. 2.47 gm of this solid were converted to the hydrochloride salt to give 1.16 gm of the title compound as light yellow crystals.

m.p.>220°C (dec)(ethyl acetate/methanol)

MS(m/e): 409(M⁺)

25 Calculated for C₂₈H₂₈N₂O·HCl: Theory: C, 75.57; H, 6.57; N, 6.30. Found: C, 75.51; H, 6.68; N, 6.52.

EXAMPLE 23

30

5-methyl-3-<1-<1,2,3,6-tetrahydro-<2-<phenyl>ethyl>-4-pyridinyl>>-1H-indole maleate

35

Using 3.0 gm (23 mMol) 5-methyl-1H-indole and 9.30 gm (46 mMol) N-phenethyl-4-piperidone, 11.64 gm of crude product were recovered as a brown oil. The oil was subjected to silica gel chromatography, eluting with dichloromethane containing 5% methanol. Fractions shown to contain product were combined and concentrated under reduced pressure to give 2.20 gm of the free base of the title compound. This solid was converted to the maleate salt to give 1.14 gm (11.5%) of the title compound as a light brown solid.

m.p.=184-187°C (ethyl acetate/methanol)

MS(m/e): 316(M⁺)

Calculated for C₂₂H₂₄N₂·C₄H₄O₄: Theory: C, 72.20; H, 6.53; N, 6.48. Found: C, 71.96; H, 6.41; N, 6.33.

40

EXAMPLE 24

5-carboxamido-3-<1-<1,2,3,6-tetrahydro-<2-<phenyl>ethyl>-4-pyridinyl>>-1H-indole maleate

45

Using 2.0 gm (12.5 mMol) 5-carboxamido-1H-indole and 5.1 gm (25 mmol) N-phenethyl-4-piperidone, 6.5 gm of crude product were recovered as a yellow solid. The solid was subjected to silica gel chromatography, eluting with dichloromethane containing 1-10% methanol. Fractions shown to contain product were combined and concentrated under reduced pressure to give 3.20 gm of the free base of the title compound. 2.20 gm of this solid was converted to the maleate salt to give 2.00 gm of the title compound as a yellow powder.

m.p.=188-189°C (ethyl acetate/methanol)

50

Calculated for C₂₂H₂₃N₃O·C₄H₄O₄: Theory: C, 67.66; H, 5.90; N, 9.10. Found: C, 67.75; H, 5.99; N, 9.11.

EXAMPLE 25

55

5-fluoro-3-<1-<2-<phenyl>ethyl>-4-piperidinyl>-1H-indole hydrochloride

To a solution of 2.0 gm (6.24 mMol) 5-fluoro-3-<1-<1,2,3,6-tetrahydro-<2-<phenyl>ethyl>-4-pyridinyl>>-1H-indole (Example 18) in 50 mL ethanol were added 1.0 gm 5% palladium on carbon and the reaction mixture was hydrogenated at room temperature with an initial hydrogen pressure of 60 p.s.i. for 18 hours. The reaction mixture was concentrated

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under reduced pressure to give a yellow oil which crystallized while standing. The residue was dissolved in methanol to which was added 0.44 mL 1N HCl and the volatiles were then removed under reduced pressure. The residue was recrystallized from methanol/ethyl acetate to give 1.02 gm (45.5%) of the title compound as a colorless solid, m.p.>210°C (dec).

5 Calculated for $C_{21}H_{23}N_2F \cdot HCl$; Theory: C, 70.28; H, 6.74; N, 7.81. Found: C, 70.03; H, 6.79; N, 7.75.
The compounds of Examples 26-31 were prepared by the procedure described in detail in Example 25.

EXAMPLE 26

10 3-<1-<2-<phenyl>ethyl>-4-piperidinyl>-1H-indole

Beginning with 1.8 gm (6 mMol) 3-<1-<1,2,3,6-tetrahydro-<2-<phenyl>ethyl>-4-pyridinyl>>-1H-indole (Example 19), 1.7 gm (93.9%) of the title compound were recovered as an off-white solid.
m.p.=122-124°C (methanol)

15 Calculated for $C_{21}H_{24}N_2$; Theory: C, 82.85; H, 7.95; N, 9.20. Found: C, 82.85; H, 8.12; N, 9.14.

EXAMPLE 27

20 5-chloro-3-<1-<2-<phenyl>ethyl>-4-piperidinyl>-1H-indole hydrochloride

Beginning with 1.986 gm (5.9 mmol) 5-chloro-3-<1-<1,2,3,6-tetrahydro-<2-<phenyl>ethyl>-4-pyridinyl>>-1H-indole (Example 20) and using 1.0 gm 5% sulfided platinum on carbon, 0.65 gm (32.5%) of the title compound were recovered as off-white crystals.
m.p.>250°C (methanol/ethyl acetate)

25 MS(m/e): 338(M⁺)
Calculated for $C_{21}H_{23}ClN_2 \cdot HCl$; Theory: C, 67.20; H, 6.44; N, 7.46. Found: C, 67.50; H, 6.56; N, 7.51.

EXAMPLE 28

30 5-methoxy-3-<1-<2-<phenyl>ethyl>-4-piperidinyl>-1H-indole hydrochloride

Beginning with 1.45 gm (4.4 mMol) 5-methoxy-3-<1-<1,2,3,6-tetrahydro-<2-<phenyl>ethyl>-4-pyridinyl>>-1H-indole (Example 21), 0.95 gm (58.2%) of the title compound were recovered as off-white crystals.
m.p.>210°C (methanol/ethyl acetate)

35 MS(m/e): 334(M⁺)
Calculated for $C_{22}H_{26}N_2O \cdot HCl$; Theory: C, 71.24; H, 7.34; N, 7.55. Found: C, 70.97; H, 7.36; N, 7.70.

EXAMPLE 29

40 5-benzyloxy-3-<1-<2-<phenyl>ethyl>-4-piperidinyl>-1H-indole hydrochloride

Beginning with 1.40 gm (3.4 mMol) 5-benzyloxy-3-<1-<1,2,3,6-tetrahydro-<2-<phenyl>ethyl>-4-pyridinyl>>-1H-indole (Example 22) and using 0.7 gm 5% sulfided platinum on carbon, 0.55 gm (36.2%) of the title compound were recovered as off-white crystals.

45 m.p.>220°C (dec)(methanol/ethyl acetate)
MS(m/e): 411(M⁺)
Calculated for $C_{28}H_{30}N_2O \cdot HCl$; Theory: C, 75.23; H, 6.99; N, 6.27. Found: C, 75.50; H, 7.24; N, 6.24.

EXAMPLE 30

50 5-methyl-3-<1-<2-<phenyl>ethyl>-4-piperidinyl>-1H-indole hydrochloride

Beginning with 1.50 gm (4.7 mMol) 5-methyl-3-<1-<1,2,3,6-tetrahydro-<2-<phenyl>ethyl>-4-pyridinyl>>-1H-indole (Example 23), 0.52 gm (31.2%) of the title compound were recovered as white crystals.

55 m.p.>225°C (methanol/ethyl acetate)
Calculated for $C_{22}H_{26}N_2 \cdot HCl$; Theory: C, 74.45; H, 7.67; N, 7.89. Found: C, 74.40; H, 7.82; N, 7.80.

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EXAMPLE 31

5-carboxamido-3-<1-<2-<phenyl>ethyl>-4-piperidinyl>-1H-indole hydrochloride

5 Beginning with 1.00 gm (2.9 mMol) 5-carboxamido-3-<1-<1,2,3,6-tetrahydro-<2-<phenyl>ethyl>-4-pyridinyl>>-1H-indole (Example 24), 0.56 gm (50.3%) of the title compound were recovered as a tan powder in two crops.
m.p. >300°C (methanol/ethyl acetate)
Calculated for $C_{22}H_{25}N_3O \cdot HCl$: Theory: C, 68.83; H, 6.83; N, 10.94. Found: C, 68.59; H, 7.00; N, 10.71.

10 EXAMPLE 32

3-<1-<2-<4-chlorophenyl>ethyl>-4-piperidinyl>-1H-indole hydrochloride

15 To a solution of 4.0 gm (20 mMol) 3-(4-piperidinyl)-1H-indole in 80 mL dimethylformamide were added 5.3 gm (50 mMol) sodium carbonate followed by the dropwise addition of a solution of 3.5 gm (20 mMol) 2-(4-chlorophenyl)ethyl chloride in 16 mL dimethylformamide. Once the addition was complete the reaction mixture was heated at 100°C under nitrogen for 18 hours. The reaction mixture was then cooled to ambient and the dimethylformamide removed under reduced pressure. The residue was dissolved in dichloromethane then washed twice with water and once with saturated aqueous sodium chloride. The remaining organics were dried over sodium sulfate and then concentrated under reduced
20 pressure to give a yellow oil. The oil was subjected to silica gel chromatography, eluting with 20:1:0.1 dichloromethane: methanol:ammonium hydroxide. Fractions shown to contain product were combined and concentrated under reduced pressure. The residue was dissolved in a minimal volume of methanol and treated with one equivalent of 1N HCl. The solution was concentrated under reduced pressure and the residue crystallized from methanol to give 1.95 gm (26.0%) of the title compound as off-white crystals, m.p.>250°C.
25 MS(m/e): 338(M⁺)
Calculated for $C_{21}H_{23}N_2Cl \cdot HCl$: Theory: C, 67.20; H, 6.45; N, 7.46. Found: C, 67.16; H, 7.42; N, 7.50.

EXAMPLE 33

30 3-<1-<2-<4-methoxyphenyl>ethyl>-4-piperidinyl>-1H-indole hydrochloride

Following the procedure described in detail in Example 32, 2.0 gm (10 mMol) 3-(4-piperidinyl)-1H-indole and 1.0 gm (10 mMol) 2-(4-methoxyphenyl)ethyl chloride were converted to 0.87 gm (23.4%) of the title compound which was recovered as colorless crystals from methanol/ethyl acetate, m.p.>250°C.

35 MS(m/e): 334(M⁺)
Calculated for $C_{22}H_{26}N_2O \cdot HCl$: Theory: C, 71.24; H, 7.34; N, 7.55. Found: C, 71.05; H, 7.16; N, 7.52.

EXAMPLE 34

40 3-<1-<1,2,3,6-tetrahydro-<2-<1-naphthyl>ethyl>-4-pyridinyl>-1H-indole

Following the procedure described in detail in Example 32, 3.97 gm (20 mMol) 3-<1-<1,2,3,6-tetrahydro->-4-pyridinyl>-1H-indole and 4.7 gm (20 mMol) 2-(1-naphthyl)ethyl chloride were converted to 2.0 gm (28.3%) of the title compound which was recovered as yellow crystals from methanol, m.p.=180-182°C.

45 MS(m/e): 352(M⁺)
Calculated for $C_{25}H_{24}N_2$: Theory: C, 85.19; H, 6.86; N, 7.95. Found: C, 85.39; H, 6.82; N, 8.09.

EXAMPLE 35

50 3-<1-<2-<1-naphthyl>ethyl>-4-piperidinyl>-1H-indole

Following the procedure described in detail in Example 25, 0.77 gm (2.19 mMol) 3-<1-<1,2,3,6-tetrahydro-<2-<1-naphthyl>ethyl>-4-pyridinyl>-1H-indole (Example 34) were converted to 0.25 gm of the title compound which was isolated as a yellow oil.

55 MS(m/e): 354(M⁺)

EXAMPLE 36

5-hydroxy-3-<1-<2-<phenyl>ethyl>-4-piperidinyl>-1H-indole hydrochloride

5 Following the procedure described in detail in Example 25, 3.0 gm (2.19 mMol) 5-benzyloxy-3-<1-<1,2,3,6-tetrahydro-<2-<phenyl>ethyl>-4-pyridinyl>>-1H-indole hydrochloride (Example 22) were converted to 1.50 gm (62%) of the title compound which was isolated as a yellow granular solid. m.p.=260°C (dec).

MS(m/e): 320(M⁺)

Calculated for C₂₁H₂₄N₂O·HCl: Theory: C, 70.67; H, 7.06; N, 7.85. Found: C, 70.43; H, 6.92; N, 7.95.

EXAMPLE 37

3-<1-<1,2,3,6-tetrahydro-<2-<phenoxy>ethyl>-4-pyridinyl>>-1H-indole hydrochloride

15 Following the procedure described in detail in Example 32, 3.97 gm (20 mMol) 3-<1-<1,2,3,6-tetrahydro>-4-pyridinyl>-1H-indole and 4.02 gm (20 mMol) β-bromophenetole were converted to 4.63 gm (65.2%) of the title compound which was recovered as a yellow solid.

m.p.=182-184°C (methanol/ethyl acetate).

MS(m/e): 318(M⁺)

20 Calculated for C₂₁H₂₂N₂O·HCl: Theory: C, 71.07; H, 6.53; N, 7.89. Found: C, 70.86; H, 6.55; N, 7.84.

EXAMPLE 38

3-<1-<1,2,3,6-tetrahydro-<3-<phenoxy>propyl>-4-pyridinyl>>-1H-indole hydrochloride

25 Following the procedure described in detail in Example 32, 3.97 gm (20 mMol) 3-<1-<1,2,3,6-tetrahydro>-4-pyridinyl>-1H-indole and 4.30 gm (20 mMol) 3-bromopropyl phenyl ether were converted to 3.33 gm (45.1%) of the title compound which was recovered as orange crystals.

m.p.=234-235°C (methanol/ethyl acetate).

30 MS(m/e): 333(M⁺)

Calculated for C₂₂H₂₄N₂O·HCl: Theory: C, 71.63; H, 6.83; N, 7.59. Found: C, 71.69; H, 6.89; N, 7.35.

EXAMPLE 39

35 3-<1-<1,2,3,6-tetrahydro-<2-<phenylthio>ethyl>-4-pyridinyl>>-1H-indole

Following the procedure described in detail in Example 32, 3.97 gm (20 mMol) 3-<1-<1,2,3,6-tetrahydro>-4-pyridinyl>-1H-indole and 3.45 gm (20 mMol) 2-chloroethyl phenyl sulfide were converted to 1.29 gm (19.3%) of the title compound which was recovered as yellow crystals.

40 m.p.=121-122°C (methanol).

MS(m/e): 334(M⁺)

Calculated for C₂₁H₂₂N₂S: Theory: C, 75.41; H, 6.65; N, 8.38. Found: C, 75.14; H, 6.44; N, 8.21.

EXAMPLE 40

45 3-<1-<2-<phenoxy>ethyl>-4-piperidinyl>-1H-indole hydrochloride

Following the procedure described in detail in Example 25, 2.0 gm (5.6 mMol) 3-<1-<1,2,3,6-tetrahydro-<2-<phenoxy>ethyl>-4-pyridinyl>>-1H-indole (Example 37) were converted to 0.92 gm (46.0%) of the title compound as an off-white solid.

m.p.=231-233°C (methanol/ethyl acetate)

MS(m/e): 320(M⁺)

Calculated for C₂₁H₂₄N₂O·HCl: Theory: C, 70.67; H, 7.06; N, 7.83. Found: C, 69.88; H, 7.07; N, 7.79.

EXAMPLE 41

3-<1-<3-<phenoxy>propyl>-4-piperidinyl>-1H-indole hydrochloride

Following the procedure described in detail in Example 25, 1.51 gm (4.1 mMol) 3-<1-<1,2,3,6-tetrahydro-<3-<phenoxy>propyl>-4-pyridinyl>>-1H-indole (Example 38) were converted to 0.13 gm (8.5%) of the title compound as a gray solid.
m.p.>250°C (dec)(methanol/ethyl acetate)
Calculated for C₂₂H₂₆N₂O·HCl: Theory: C, 71.24; H, 7.34; N, 7.55. Found: C, 71.49; H, 7.42; N, 7.76.

EXAMPLE 42

3-<1-<2-<phenylthio>ethyl>-4-piperidinyl>-1H-indole

Following the procedure described in detail in Example 32, 2.0 gm (10 mMol) 3-<1-<4-piperidinyl>-1H-indole and 1.73 gm (10 mMol) 2-chloroethyl phenyl sulfide were converted to 1.28 gm (38.0%) of the title compound which was recovered as a yellow oil.
MS(m/e): 336(M⁺)
Calculated for C₂₁H₂₄N₂S: Theory: C, 74.96; H, 7.19; N, 8.33. Found: C, 74.95; H, 7.17; N, 8.43.

EXAMPLE 43

3-<1-<1,2,3,6-tetrahydro-<4-<phenyl>butyl>-4-pyridinyl>>-1H-indole hydrochloride

Following the procedure described in detail in Example 32, 3.97 gm (20 mMol) 3-<1-<1,2,3,6-tetrahydro->-4-pyridinyl>-1H-indole and 3.37 gm (20 mMol) 1-chloro-4-phenylbutane were converted to 3.68 gm (50.1%) of the title compound which was recovered as yellow crystals.
m.p.>220°C (dec)(ethanol).
MS(m/e): 330(M⁺)
Calculated for C₂₃H₂₆N₂·HCl: Theory: C, 75.29; H, 7.42; N, 7.63. Found: C, 75.49; H, 7.55; N, 7.86.

EXAMPLE 44

3-<1-<1,2,3,6-tetrahydro-<benzyl>-4-pyridinyl>>-1H-indole hydrochloride

Following the procedure described in detail in Example 32, 3.97 gm (20 mMol) 3-<1-<1,2,3,6-tetrahydro->-4-pyridinyl>-1H-indole and 2.4 mL (20 mMol) benzyl bromide were converted to 3.93 gm (60.5%) of the title compound which was recovered as a brown solid.
m.p.=159°C (dec)(methanol/ethyl acetate).
MS(m/e): 288(M⁺)
Calculated for C₂₀H₂₀N₂·HCl: Theory: C, 73.95; H, 6.52; N, 8.62. Found: C, 74.06; H, 6.49; N, 8.68.

EXAMPLE 45

3-<1-<benzyl>-4-piperidinyl>-1H-indole

Following the procedure described in detail in Example 32, 0.94 gm (4.7 mMol) 3-<1-<4-piperidinyl>-1H-indole and 0.803 gm (4.7 mMol) benzyl bromide were converted to 0.41 gm (30.0%) of the title compound which was recovered as a yellow oil.
MS(m/e): 290(M⁺)
Calculated for C₂₀H₂₂N₂: Theory: C, 82.72; H, 7.64; N, 9.65. Found: C, 82.44; H, 7.53; N, 9.76.

EXAMPLE 46

3-<1-<4-<phenyl>butyl>-4-piperidinyl>-1H-indole hydrochloride

Following the procedure described in detail in Example 25, 1.89 gm (5.2 mMol) 3-<1-<1,2,3,6-tetrahydro-<4-<phenyl>butyl>-4-pyridinyl>>-1H-indole hydrochloride (Example 43) were converted to 1.19 gm (62.0%) of the title com-

pound as a yellow solid.

m.p.=233-234°C (methanol/ethyl acetate)

Calculated for C₂₃H₂₈N₂·HCl: Theory: C, 74.88; H, 7.92; N, 7.59. Found: C, 74.61; H, 7.91; N, 7.59.

5 EXAMPLE 47

3-<1-<1,2,3,6-tetrahydro-<3-<phenyl>propyl>-4-pyridinyl>-1H-indole hydrochloride

Following the procedure described in detail in Example 32, 1.98 gm (10 mMol) 3-<1-<1,2,3,6-tetrahydro->-4-pyridinyl>-1H-indole and 1.99 gm (10 mMol) 1-bromo-3-phenylpropane were converted to 1.51 gm (42.8%) of the title compound which was recovered as orange crystals.

m.p.=215-217°C (ethanol).

MS(m/e): 316(M⁺)

Calculated for C₂₂H₂₄N₂·HCl: Theory: C, 74.88; H, 7.14; N, 7.94. Found: C, 74.79; H, 7.34; N, 7.87.

15

EXAMPLE 48

3-<1-<3-<phenyl>propyl>-4-piperidinyl>-1H-indole hydrochloride

20 Following the procedure described in detail in Example 32, 1.20 gm (6.0 mMol) 3-<1-<4-piperidinyl>-1H-indole and 1.19 gm (6.0 mMol) 1-bromo-3-phenylpropane were converted to 0.83 gm (39.0%) of the title compound which was recovered as off-white crystals.

m.p.=239-241°C (methanol)

MS(m/e): 318(M⁺)

25

Calculated for C₂₂H₂₆N₂·HCl: Theory: C, 74.45; H, 7.67; N, 7.89. Found: C, 74.17; H, 7.70; N, 8.16.

To demonstrate the use of the compounds of this invention in the treatment of migraine, their ability to bind to the 5-HT_{1F} receptor subtype was determined. The ability of the compounds of this invention to bind to the 5-HT_{1F} receptor subtype was measured essentially as described in N. Adham, et al., *Proceedings of the National Academy of Sciences (USA)*, **90**, 408-412 (1993).

30 Membrane Preparation: Membranes were prepared from transfected Ltk- cells which were grown to 100% confluence. The cells were washed twice with phosphate-buffered saline, scraped from the culture dishes into 5 mL of ice-cold phosphate-buffered saline, and centrifuged at 200 x g for 5 minutes at 4°C. The pellet was resuspended in 2.5 mL of ice-cold Tris buffer (20 mM Tris HCl, pH=7.4 at 23°C, 5 mM EDTA) and homogenized with a Wheaton tissue grinder. The lysate was subsequently centrifuged at 200 x g for 5 minutes at 4°C to pellet large fragments which were discarded. The supernatant was collected and centrifuged at 40,000 x g for 20 minutes at 4°C. The pellet resulting from this centrifugation was washed once in ice-cold Tris wash buffer and resuspended in a final buffer containing 50 mM Tris HCl and 0.5 mM EDTA, pH=7.4 at 23°C. Membrane preparations were kept on ice and utilized within two hours for the radioligand binding assays. Protein concentrations were determined by the method of Bradford (*Anal. Biochem.*, **72**, 248-254 (1976)).

40 Radioligand Binding: [³H]-5-HT binding was performed using slight modifications of the 5-HT_{1D} assay conditions reported by Herrick-Davis and Titeler (*J. Neurochem.*, **50**, 1624-1631 (1988)) with the omission of masking ligands. Radioligand binding studies were achieved at 37°C in a total volume of 250 µL of buffer (50 mM Tris, 10 mM MgCl₂, 0.2 mM EDTA, 10 µM pargyline, 0.1% ascorbate, pH=7.4 at 37°C) in 96 well microtiter plates. Saturation studies were conducted using [³H]5-HT at 12 different concentrations ranging from 0.5 nM to 100 nM. Displacement studies were

45 performed using 4.5-5.5 nM [³H]5-HT. The binding profile of drugs in competition experiments was accomplished using 10-12 concentrations of compound. Incubation times were 30 minutes for both saturation and displacement studies based upon initial investigations which determined equilibrium binding conditions. Nonspecific binding was defined in the presence of 10 µM 5-HT. Binding was initiated by the addition of 50 µL membrane homogenates (10-20 µg). The reaction was terminated by rapid filtration through presoaked (0.5% polyethyleneimine) filters using 48R Cell Brandel

50 Harvester (Gaithersburg, MD). Subsequently, filters were washed for 5 seconds with ice cold buffer (50 mM Tris HCl, pH=7.4 at 4°C), dried and placed into vials containing 2.5 mL Readi-Safe (Beckman, Fullerton, CA) and radioactivity was measured using a Beckman LS 5000TA liquid scintillation counter. The efficiency of counting of [³H]5-HT averaged between 45-50%. Binding data was analyzed by computer-assisted nonlinear regression analysis (Accufit and Accu-

55 comp, Lunden Software, Chagrin Falls, OH). IC₅₀ values were converted to K_i values using the Cheng-Prusoff equation (*Biochem. Pharmacol.*, **22**, 3099-3108 (1973)). All experiments were performed in triplicate. The results of these binding experiments are summarized in Table I.

TABLE I

	COMPOUND OF EXAMPLE NUMBER	5-HT _{1F} BINDING K _i (nM)	COMPOUND OF EXAMPLE NUMBER	5-HT _{1F} BINDING K _i (nM)
5	1	29.5	24	23.6
	2	55.5	25	29.6
	3	31.0	26	52.1
	4	35.8	27	45.5
	5	35.2	28	39.2
	6	11.7	29	17.2
	7	73.3	30	37.8
	8	45.0	31	36.9
	9	29.7	32	52.1
	10	67.6	33	127.4
10	11	34.0	34	38%*
	12	21.1	35	76.7
	13	128.0	36	2.5
	14	184.7	37	413.0
	15	843.6	38	136.0
	16	64.3	39	34%*
15	17	16.1	40	191.3
	18	48.3	41	91.4
	19	81.1	42	342.3
	20	38.8	43	546.6
	21	33.9	44	396.0
	22	62%*	45	240.4
20	23	28.3	46	20.4
	COMPOUND OF EXAMPLE NUMBER	5-HT _{1F} BINDING K _i (nM)	COMPOUND OF EXAMPLE NUMBER	5-HT _{1F} BINDING K _i (nM)
25	47	62%*	48	50%*
	=% displacement at 1000 nM			

As was reported by R. L. Weinshank, *et al.*, WO93/14201, the 5-HT_{1F} receptor is functionally coupled to a G-protein as measured by the ability of serotonin and serotonergic drugs to inhibit forskolin stimulated cAMP production in NIH3T3 cells transfected with the 5-HT_{1F} receptor. Adenylate cyclase activity was determined using standard techniques. A maximal effect is achieved by serotonin. An E_{max} is determined by dividing the inhibition of a test compound by the maximal effect and determining a percent inhibition. (N. Adham, *et al.*, *supra*; R.L. Weinshank, *et al.*, *Proceedings of the National Academy of Sciences (USA)*, 89, 3630-3634 (1992)), and the references cited therein.

Measurement of cAMP formation

Transfected NIH3T3 cells (estimated Bmax from one point competition studies=488 fmol/mg of protein) were incubated in DMEM, 5 mM theophylline, 10 mM HEPES (4-[2-hydroxyethyl]-1-piperazineethanesulfonic acid) and 10 μM pargyline for 20 minutes at 37°C, 5% CO₂. Drug dose-effect curves were then conducted by adding 6 different final concentrations of drug, followed immediately by the addition of forskolin (10 μM). Subsequently, the cells were incubated for an additional 10 minutes at 37°C, 5% CO₂. The medium was aspirated and the reaction was stopped by the addition of 100 mM HCl. To demonstrate competitive antagonism, a dose-response curve for 5-HT was measured in parallel, using a fixed dose of methiothepin (0.32 μM). The plates were stored at 4°C for 15 minutes and then centrifuged for 5 minutes at 500 x g to pellet cellular debris, and the supernatant was aliquoted and stored at -20°C before assessment of cAMP formation by radioimmunoassay (cAMP radioimmunoassay kit; Advanced Magnetics, Cambridge, MA). Radioactivity was quantified using a Packard COBRA Auto Gamma counter, equipped with data reduction software. All of the compounds exemplified were tested and found to be agonists at the 5-HT_{1F} receptor in the cAMP assay.

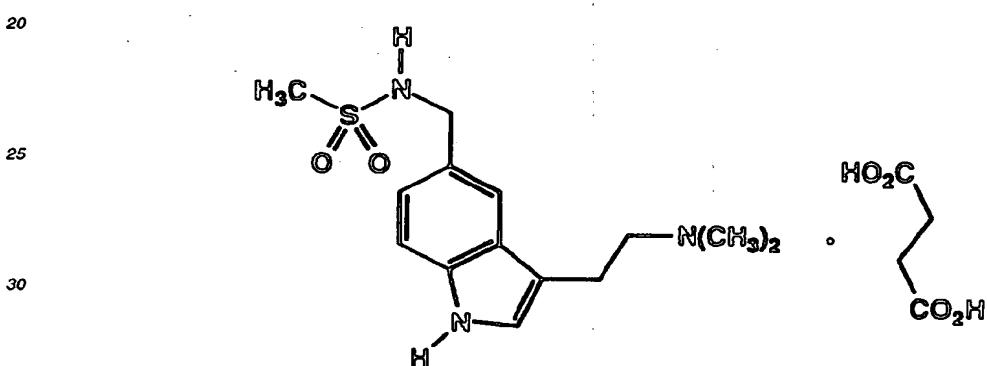
The discovery that the pain associated with migraine and associated disorders is inhibited by agonists of the 5-HT_{1F} receptor required the analysis of data from diverse assays of pharmacological activity. To establish that the 5-HT_{1F}

receptor subtype is responsible for mediating neurogenic meningeal extravasation which leads to the pain of migraine, the binding affinity of a panel of compounds to serotonin receptors was measured first, using standard procedures. For example, the ability of a compound to bind to the 5-HT_{1F} receptor subtype was performed as described *supra*. For comparison purposes, the binding affinities of compounds to the 5-HT_{1D α} , 5-HT_{1D β} , 5-HT_{1E} and 5-HT_{1F} receptors were also determined as described *supra*, except that different cloned receptors were employed in place of the 5-HT_{1F} receptor clone employed therein. The same panel was then tested in the cAMP assay to determine their agonist or antagonist character. Finally, the ability of these compounds to inhibit neuronal protein extravasation, a functional assay for migraine pain, was measured.

The panel of compounds used in this study represents distinct structural classes of compounds which were shown to exhibit a wide range of affinities for the serotonin receptors assayed. Additionally, the panel compounds were shown to have a wide efficacy range in the neuronal protein extravasation assay as well. The panel of compounds selected for this study are described below.

Compound I

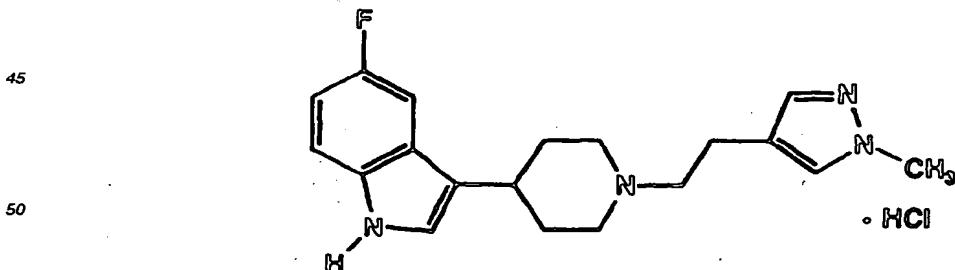
3-[2-(dimethylamino)ethyl]-N-methyl-1H-indole-5-methanesulfonamide butane-1,4-dioate (1:1) (Sumatriptan succinate)



Sumatriptan succinate is commercially available as Imitrex™ or may be prepared as described in United States Patent 5,037,845, issued August 6, 1991, which is herein incorporated by reference.

Compound II

5-fluoro-3-<1-<2-<1-methyl-1H-pyrazol-4-yl>ethyl>-4-piperidinyl>-1H-indole hydrochloride



Compound II is available by the following procedure.

2-(1-methyl-3-pyrazolo)-1-ethanol

To a mixture of 200 gm (2.85 mole) 2,3-dihydrofuran and 800 mL (4.81 mole) triethylorthoformate were added 0.8

mL (6.5 mMol) boron trifluoride diethyl etherate dropwise. After an initial exotherm the reaction mixture was allowed to stir at ambient temperature for four days. To the reaction mixture was then added 4.0 gm potassium carbonate and the reaction mixture was distilled under 6.0 mm Hg. Fractions distilling between 60°C and 130°C were collected to give 261.64 gm (42.1%) of a light yellow oil.

5 MS(m/e): 219(M⁺)

To a solution of 87.2 gm (0.40 mole) of the previously prepared yellow oil in 787 mL 1N HCl were added 21.3 mL (0.40 mole) methyl hydrazine and the reaction mixture was stirred at reflux for four hours. The reaction mixture was cooled to ambient temperature and the volatiles were removed under reduced pressure. The residual oil was treated with 2N NaOH until basic and the aqueous extracted well with dichloromethane. The combined organic extracts were dried over sodium sulfate and concentrated under reduced pressure to give 32.15 gm (64.5%) of the title compound as a brown oil.

10 MS(m/e): 126(M⁺)

1H-NMR(DMSO-d₆): δ7.45 (s, 1H); 7.25 (s, 1H); 4.65 (t, 1H); 3.75 (s, 3H); 3.55 (m, 2H); 2.55 (t, 2H).

15 1-methyl-4-(2-methanesulfonyloxyethyl)pyrazole

To a solution of 16.0 gm (127 mMol) 2-(1-methyl-3-pyrazolo)-1-ethanol and 27 mL (193 mMol) triethylamine in 550 mL tetrahydrofuran were added 10.8 mL (140 mMol) methanesulfonyl chloride with icebath cooling. Once the addition was complete, the reaction mixture was stirred at ambient for 4 hours. The volatiles were then removed under reduced pressure and the residue partitioned between water and dichloromethane. The organic phase was washed with water followed by saturated aqueous sodium chloride and the remaining organics dried over sodium sulfate. The solvent was removed under reduced pressure to give a crude yield of 28.4 gm of the title compound as a brown oil. The product was used without further purification.

25 5-fluoro-3-[1,2,3,6-tetrahydro-4-pyridyl]-1H-indole

To a solution of 74 gm potassium hydroxide in 673 mL methanol were added 10.0 gm (74 mMol) 5-fluoroindole and 23.3 gm (151 mMol) 4-piperidone-HCl-H₂O. The reaction mixture was stirred at reflux for 18 hours. The reaction mixture was diluted with 1.3 L of water and the resulting precipitate recovered by filtration and dried under reduced pressure to give 10.75 gm (67.2%) of 5-fluoro-3-[1,2,5,6-tetrahydro-4-pyridyl]-1H-indole as a yellow solid.

30 5-fluoro-3-(4-piperidinyl)-1H-indole

To a solution of 10.75 gm (50 mMol) 5-fluoro-3-[1,2,5,6-tetrahydro-4-pyridyl]-1H-indole in 500 mL ethanol were added 2.0 gm 5% palladium on carbon and the reaction mixture hydrogenated at ambient temperature for 18 hours at an initial hydrogen pressure of 60 p.s.i. The reaction mixture was then filtered through a pad of celite and the filtrate concentrated under reduced pressure to give an off-white solid. The solid was recrystallized from methanol to give 8.31 gm (76.2%) of the title compound as a colorless solid. m.p.=229-230°C.

35 MS(m/e): 218(M⁺)

40 Calculated for C₁₃H₁₅N₂F: Theory: C, 71.53; H, 6.93; N, 12.83. Found: C, 71.81; H, 7.02; N, 12.80.

Alkylation

To a solution of 2.0 gm (9.2 mMol) 5-fluoro-3-(4-piperidinyl)-1H-indole and 2.4 gm (23 mMol) sodium carbonate in 50 mL dimethylformamide were added 1.87 gm (9.2 mMol) 1-methyl-4-(2-methanesulfonyloxyethyl)pyrazole in 5 mL dimethylformamide. The reaction mixture was stirred at 100°C for 18 hours. The reaction mixture was cooled to ambient and the solvent removed under reduced pressure. The residue was partitioned between dichloromethane and water and the phases separated. The organic phase was washed well with water followed by saturated aqueous sodium chloride. The remaining organic phase was dried over sodium sulfate and concentrated under reduced pressure. The residual oil was subjected to silica gel chromatography, eluting with 20:1 dichloromethane:methanol. Fractions shown to contain the desired compound were combined and concentrated under reduced pressure to give a yellow oil. The oil was converted to the hydrochloride salt and was crystallized from ethyl acetate/methanol. 1.61 gm (51.1%) of Compound II were recovered as colorless crystals.

m.p.=239°C.

55 MS(m/e): 326(M⁺)

Calculated for C₁₉H₂₃N₄F·HCl: Theory: C, 62.89; H, 6.67; N, 15.44. Found: C, 62.80; H, 6.85; N, 15.40.

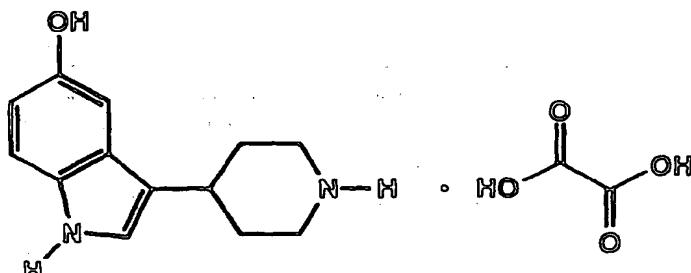
Compound III

5-hydroxy-3-(4-piperidinyl)-1H-indole oxalate

5

10

15



Compound III is available by the following procedure.

5-benzyloxy-3-[1,2,5,6-tetrahydro-4-pyridinyl]-1H-indole

20

Starting with 5.0 gm (22 mMol) 5-benzyloxyindole and 6.88 gm (45 mMol) 4-piperidone-HCl·H₂O, 6.53 gm (97.6%) of 5-benzyloxy-3-[1,2,5,6-tetrahydro-4-pyridinyl]-1H-indole were recovered as a light yellow solid by the procedure described in Preparation I. The material was used in the subsequent step without further purification.

25

Hydrogenation/Hydrogenolysis

To a solution of 1.23 gm (4 mMol) 5-benzyloxy-3-[1,2,5,6-tetrahydro-4-pyridinyl]-1H-indole in 50 mL 1:1 tetrahydrofuran:ethanol were added 0.3 gm 5% palladium on carbon and the reaction mixture hydrogenated at ambient temperature for 18 hours with an initial hydrogen pressure of 60 p.s.i. The reaction mixture was then filtered through a celite pad and the filtrate concentrated under reduced pressure. The residue was converted to the oxalate salt and 0.98 gm (80.0%) of Compound III were recovered as a brown foam.

m.p.=67°C

MS(m/e): 216(M⁺)Calculated for C₁₃H₁₆N₂O·C₂H₂O₄: Theory: C, 58.81; H, 5.92; N, 9.14. Found: C, 58.70; H, 5.95; N, 9.39.

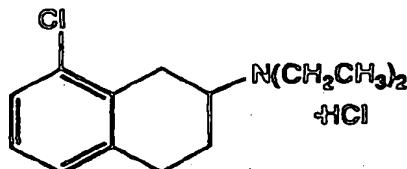
35

Compound IV

8-chloro-2-diethylamino-1,2,3,4-tetrahydronaphthalene hydrochloride

40

45



Compound IV is available by the following procedure.

50

8-chloro-2-tetralone

A mixture of 30.0 gm (0.176 mole) of *o*-chlorophenyl-acetic acid and 40.0 mL of thionyl chloride was stirred at ambient temperature for 18 hours. The volatiles were then removed in vacuo to give 32.76 gm (99.0 %) of *o*-chlorophenylacetyl chloride as a transparent, pale yellow, mobile liquid.

55

NMR(CDCl₃): 7.5-7.1 (m, 4H), 4.2 (s, 2H).

To a slurry of 46.5 gm (0.348 mole) AlCl₃ in 400 mL dichloromethane at -78°C was added a solution of 32.76 gm (0.174 mole) of the previously prepared *o*-chlorophenylacetyl chloride in 100 mL dichloromethane dropwise over 1 hour. The dry ice/acetone bath then was replaced with an ice/water bath and ethylene was bubbled into the reaction

mixture during which time the temperature rose to 15°C. The ethylene addition was discontinued at the end of the exotherm and the reaction mixture was stirred at about 5°C for 4 hours. Ice was then added to the reaction mixture to destroy aluminum complexes. Upon termination of the exotherm, the reaction mixture was diluted with 500 mL of water and stirred vigorously until all solids had dissolved. The phases were separated and the organic phase was washed with 3x400 mL 1N hydrochloric acid and 2x400 mL saturated aqueous sodium bicarbonate. The remaining organic phase was then dried over sodium sulfate and concentrated in vacuo to give a pale orange residue. The residue was dissolved in 1:1 hexane:diethyl ether and was poured over a flash silica column which was then eluted with 1:1 hexane:diethyl ether to give a light yellow residue which was crystallized from 4:1 hexane:diethyl ether to give 10.55 gm of the title compound. NMR(CDCl₃): 7.5-7.2 (m, 3H), 3.7 (s, 2H), 3.3-3.0 (t, J=7 Hz, 2H), 2.8-2.4 (t, J=7 Hz, 2H).
 MS: 180(60), 165(9), 138(100), 117(52), 115(50), 103(48), 89(20), 76(25), 74(18), 63(30), 57(9), 52(28), 51(20), 42(6), 39(32).
 IR(nujol mull): 2950 cm⁻¹, 2927 cm⁻¹, 1708 cm⁻¹, 1464 cm⁻¹, 1450 cm⁻¹, 1169 cm⁻¹, 1141 cm⁻¹.

Reductive Amination

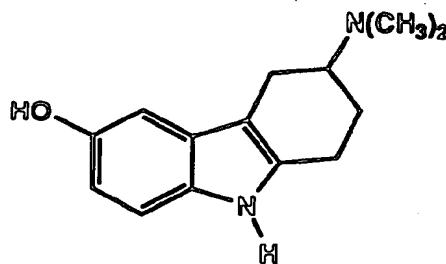
To a solution of 0.5 gm (2.78 mMol) 8-chloro-2-tetralone in 25 mL cyclohexane were added 1.4 mL (13.9 mMol) diethylamine followed by 0.1 gm p-toluenesulfonic acid monohydrate. The reaction mixture was then heated at reflux with constant water removal (Dean-Stark Trap) for 18 hours. The reaction mixture was then cooled to ambient and the volatiles removed under reduced pressure. The residue was then dissolved in 15 mL methanol to which were then added 1.5 mL acetic acid followed by the portionwise addition of 0.5 gm sodium borohydride. The reaction mixture was then stirred for 1 hour at ambient.

The reaction mixture was then diluted with 20 mL 10% HCl and stirred for an additional hour. The mixture was then extracted with diethyl ether and the remaining aqueous phase was poured over ice, made basic with ammonium hydroxide and extracted well with dichloromethane. These extracts were combined, dried over sodium sulfate and concentrated under reduced pressure. The residue was redissolved in dichloromethane and subjected to chromatography over basic alumina, eluting with dichloromethane. Fractions shown to contain product were combined and concentrated under reduced pressure. The residual oil was dissolved in diethyl ether and the solution saturated with hydrogen chloride. The viscous residue was crystallized from acetone/diethyl ether to give 0.20 gm (23.2%) of Compound IV as colorless crystals.

m.p.=158-159°C
 MS(m/e): 273
 Calculated for C₁₄H₂₁NCl·HCl: Theory: C, 61.32; H, 7.72; N, 5.11. Found: C, 61.62; H, 7.94; N, 5.03.

Compound V

6-hydroxy-3-dimethylamino-1,2,3,4-tetrahydrocarbazole



Compound V is available by the following procedure.

4-dimethylamino-1-cyclohexanone ethylene ketal

To a solution of 5.0 gm (32 mMol) 1,4-cyclohexanedione mono-ethylene ketal and 10.80 gm (240 mMol) dimethylamine were added 2.0 mL acetic acid and the mixture was stirred at 0°C for 1.5 hours. To this solution were then added 3.62 gm (58 mMol) sodium cyanoborohydride and the reaction stirred for an additional hour at ambient. The pH of the reaction mixture was adjusted to ~7 with 16 mL acetic acid and stirred 18 hours at ambient. The volatiles were removed under reduced pressure and the residue dissolved in cold 5% tartaric acid solution and then the aqueous phase was made basic with 5N sodium hydroxide. This aqueous phase was extracted well with dichloromethane.

These organic extracts were combined and concentrated under reduced pressure to give 5.04 gm (85%) of the title compound as an oil.

4-dimethylamino-1-cyclohexanone

5 4.96 gm (26.8 mMol) 4-dimethylamino-1-cyclohexanone ethylene ketal were dissolved in 50 mL formic acid and the solution stirred at reflux for 18 hours. The reaction mixture was then cooled to ambient and the volatiles removed under reduced pressure to give 3.78 gm (100%) of the title compound.

10 6-benzyloxy-3-dimethylamino-1,2,3,4-tetrahydrocarbazole

To a solution of 3.78 gm (26.8 mMol) 4-dimethylamino-1-cyclohexanone and 6.69 gm (26.8 mMol) 4-benzyloxy-phenylhydrazine hydrochloride in 50-mL ethanol were added 2.17 mL (26.8 mMol) pyridine. To this solution were added 5x10 mL portions of water and the reaction mixture then stored at 0°C for 18 hours. The reaction mixture was then diluted with an additional 50 mL of water and the mixture extracted well with dichloromethane. The combined organic extracts were dried over sodium sulfate and the volatiles removed under reduced pressure. The residual oil was subjected to flash silica gel chromatography, eluting with 9:1 chloroform:methanol. Fractions shown to contain the desired product were combined and concentrated under reduced pressure to give 2.14 gm (24.9%) of the title compound.

20 Hydrogenolysis

To a solution of 2.14 gm (6.7 mMol) 6-benzyloxy-3-dimethylamino-1,2,3,4-tetrahydrocarbazole in 50 mL ethanol were added 0.20 gm 10% palladium on carbon and the reaction mixture was hydrogenated at ambient temperature with an initial hydrogen pressure of 40 p.s.i. After 5 hours an additional charge of 0.20 gm 10% palladium on carbon were added and the reaction mixture repressurized with hydrogen to 40 p.s.i. for 4 hours. The reaction mixture was then filtered through a pad of celite and the filtrate concentrated under reduced pressure. The residue was subjected to Florisil chromatography, eluting with 9:1 chloroform:methanol. Fractions shown to contain the desired compound were combined and concentrated under reduced pressure. The residue was again subjected to Florisil chromatography, eluting with a gradient consisting of chloroform containing 2-10% methanol. Fractions shown to contain product were combined and concentrated under reduced pressure to give Compound V as a crystalline solid.

MS(m/e): 230(M⁺)

Calculated for C₁₄H₁₈N₂O: Theory: C, 73.01; H, 7.88; N, 12.16. Found: C, 72.75; H, 7.83; N, 11.97.

35 Binding Assays

The binding affinities of compounds for various serotonin receptors were determined essentially as described above except that different cloned receptors are employed in place of the 5-HT_{1F} receptor clone employed therein. The results of these binding experiments are summarized in Table II.

40 TABLE II

BINDING TO SEROTONIN (5-HT ₁) RECEPTOR SUBTYPES (K _i , nM)				
Compound	5-HT _{1Dα}	5-HT _{1Dβ}	5-HT _{1E}	5-HT _{1F}
I	4.8	9.6	2520.0	25.7
II	21.7	53.6	50.3	2.5
III	163.2	196.5	3.9	22.0
IV	13.5	145.3	813.0	129.2
V	791.0	1683.0	73.6	10.3

50 cAMP Formation

All of the compounds of the panel were tested in the cAMP formation assay described *supra* and all were found to be agonists of the 5-HT_{1F} receptor.

55 Protein Extravasation

Harlan Sprague-Dawley rats (225-325 g) or guinea pigs from Charles River Laboratories (225-325 g) were anes-

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thetized with sodium pentobarbital intraperitoneally (65 mg/kg or 45 mg/kg respectively) and placed in a stereotaxic frame (David Kopf Instruments) with the incisor bar set at -3.5 mm for rats or -4.0 mm for guinea pigs. Following a midline sagittal scalp incision, two pairs of bilateral holes were drilled through the skull (6 mm posteriorly, 2.0 and 4.0 mm laterally in rats; 4 mm posteriorly and 3.2 and 5.2 mm laterally in guinea pigs, all coordinates referenced to bregma).

5 Pairs of stainless steel stimulating electrodes (Rhodes Medical Systems, Inc.) were lowered through the holes in both hemispheres to a depth of 9 mm (rats) or 10.5 mm (guinea pigs) from dura.

The femoral vein was exposed and a dose of the test compound was injected intravenously (1 mL/kg). Approximately 7 minutes later, a 50 mg/kg dose of Evans Blue, a fluorescent dye, was also injected intravenously. The Evans Blue complexed with proteins in the blood and functioned as a marker for protein extravasation. Exactly 10 minutes post-injection of the test compound, the left trigeminal ganglion was stimulated for 3 minutes at a current intensity of 1.0 mA (5 Hz, 4 msec duration) with a Model 273 potentiostat/ galvanostat (EG&G Princeton Applied Research).

10 Fifteen minutes following stimulation, the animals were killed and exsanguinated with 20 mL of saline. The top of the skull was removed to facilitate the collection of the dural membranes. The membrane samples were removed from both hemispheres, rinsed with water, and spread flat on microscopic slides. Once dried, the tissues were coverslipped with a 70% glycerol/water solution.

15 A fluorescence microscope (Zeiss) equipped with a grating monochromator and a spectrophotometer was used to quantify the amount of Evans Blue dye in each sample. An excitation wavelength of approximately 535 nm was utilized and the emission intensity at 600 nm was determined. The microscope was equipped with a motorized stage and also interfaced with a personal computer. This facilitated the computer-controlled movement of the stage with 20 fluorescence measurements at 25 points (500 μ m steps) on each dural sample. The mean and standard deviation of the measurements was determined by the computer.

20 The extravasation induced by the electrical stimulation of the trigeminal ganglion was an ipsilateral effect (i.e., occurs only on the side of the dura in which the trigeminal ganglion was stimulated). This allows the other (unstimulated) half of the dura to be used as a control. The ratio of the amount of extravasation in the dura from the stimulated side compared to the unstimulated side dura was calculated. Saline controls yielded a ratio of approximately 2.0 in rats and 1.8 in guinea pigs. In contrast, a compound which effectively prevented the extravasation in the dura from the stimulated side would have a ratio of approximately 1.0. A dose-response curve was generated and the dose that inhibited the extravasation by 50% (ID_{50}) was approximated. This data is presented in Table III.

30

Table III

Inhibition of Protein Extravasation (ID_{50} mMol/kg)	
Compound	I.v. ID_{50} (mMol/kg)
I	2.6×10^{-8}
II	8.6×10^{-10}
III	8.9×10^{-9}
IV	1.2×10^{-7}
V	8.7×10^{-9}

35

To determine the relationship of binding at various serotonin receptors to inhibition of neuronal protein extravasation, the binding affinity of all of the compounds to each of the 5-HT_{1D α} , 5-HT_{1D β} , 5-HT_{1E} and 5-HT_{1F} receptors was plotted against their ID_{50} in the protein extravasation model. A linear regression analysis was performed on each set of data and a correlation factor, R², calculated. The results of this analysis are summarized in Table IV.

40

Table IV

Correlation Factor (R ²) for Specific 5-HT ₁ Subtype Binding Affinity vs Inhibition of Protein Extravasation	
5-HT ₁ Subtype	Correlation Factor (R ²)
5-HT _{1Dα}	0.07
5-HT _{1Dβ}	0.001
5-HT _{1E}	0.31
5-HT _{1F}	0.94

45

An ideally linear relationship would generate a correlation factor of 1.0, indicating a cause and effect relationship between the two variables. The experimentally determined correlation factor between inhibition of neuronal protein extravasation and 5-HT_{1F} binding affinity is 0.94. This nearly ideal dependence of the ID_{50} in the protein extravasation

model on binding affinity to the 5-HT_{1F} receptor clearly demonstrates that the 5-HT_{1F} receptor mediates the inhibition of protein extravasation resulting from stimulation of the trigeminal ganglia.

While it is possible to administer a compound employed in the methods of this invention directly without any formulation, the compounds are usually administered in the form of pharmaceutical compositions comprising a pharmaceutically acceptable excipient and at least one active ingredient. These compositions can be administered by a variety of routes including oral, rectal, transdermal, subcutaneous, intravenous, intramuscular, and intranasal. Many of the compounds employed in the methods of this invention are effective as both injectable and oral compositions. Such compositions are prepared in a manner well known in the pharmaceutical art and comprise at least one active compound. See, e.g., REMINGTON'S PHARMACEUTICAL SCIENCES, (16th ed. 1980).

In making the compositions employed in the present invention the active ingredient is usually mixed with an excipient, diluted by an excipient or enclosed within such a carrier which can be in the form of a capsule, sachet, paper or other container. When the excipient serves as a diluent, it can be a solid, semi-solid, or liquid material, which acts as a vehicle, carrier or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), ointments containing for example up to 10% by weight of the active compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions, and sterile packaged powders.

In preparing a formulation, it may be necessary to mill the active compound to provide the appropriate particle size prior to combining with the other ingredients. If the active compound is substantially insoluble, it ordinarily is milled to a particle size of less than 200 mesh. If the active compound is substantially water soluble, the particle size is normally adjusted by milling to provide a substantially uniform distribution in the formulation, e.g. about 40 mesh.

Some examples of suitable excipients include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, water, syrup, and methyl cellulose. The formulations can additionally include: lubricating agents such as talc; magnesium stearate, and mineral oil; wetting agents; emulsifying and suspending agents; preserving agents such as methyl- and propylhydroxybenzoates; sweetening agents; and flavoring agents. The compositions of the invention can be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient by employing procedures known in the art.

The compositions are preferably formulated in a unit dosage form, each dosage containing from about 0.05 to about 100 mg, more usually about 1.0 to about 30 mg, of the active ingredient. The term "unit dosage form" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient.

The active compounds are generally effective over a wide dosage range. For examples, dosages per day normally fall within the range of about 0.01 to about 30 mg/kg of body weight. In the treatment of adult humans, the range of about 0.1 to about 15 mg/kg/day, in single or divided dose, is especially preferred. However, it will be understood that the amount of the compound actually administered will be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound or compounds administered, the age, weight, and response of the individual patient, and the severity of the patient's symptoms, and therefore the above dosage ranges are not intended to limit the scope of the invention in any way. In some instances dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed without causing any harmful side effect, provided that such larger doses are first divided into several smaller doses for administration throughout the day.

Formulation Example 1

Hard gelatin capsules containing the following ingredients are prepared:

Ingredient	Quantity (mg/capsule)
Compound of Example 24	30.0
Starch	305.0
Magnesium stearate	5.0

The above ingredients are mixed and filled into hard gelatin capsules in 340 mg quantities.

Formulation Example 2

A tablet formula is prepared using the ingredients below:

Ingredient	Quantity (mg/tablet)
Compound of Example 29	25.0
Cellulose, microcrystalline	200.0
Colloidal silicon dioxide	10.0
Stearic acid	5.0

The components are blended and compressed to form tablets, each weighing 240 mg.

Formulation Example 3

A dry powder inhaler formulation is prepared containing the following components:

Ingredient	Weight %
Compound of Example 6	5
Lactose	95

The active mixture is mixed with the lactose and the mixture is added to a dry powder inhaling appliance.

Formulation Example 4

Tablets, each containing 30 mg of active ingredient, are prepared as follows:

Ingredient	Quantity (mg/tablet)
Compound of Example 17	30.0 mg
Starch	45.0 mg
Microcrystalline cellulose	35.0 mg
Polyvinylpyrrolidone (as 10% solution in water)	4.0 mg
Sodium carboxymethyl starch	4.5 mg
Magnesium stearate	0.5 mg
Talc	1.0 mg
Total	<u>120 mg</u>

The active ingredient, starch and cellulose are passed through a No. 20 mesh U.S. sieve and mixed thoroughly. The solution of polyvinylpyrrolidone is mixed with the resultant powders, which are then passed through a 16 mesh U.S. sieve. The granules so produced are dried at 50-60°C and passed through a 16 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate, and talc, previously passed through a No. 30 mesh U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each weighing 120 mg.

Formulation Example 5

Capsules, each containing 40 mg of medicament are made as follows:

Ingredient	Quantity (mg/capsule)
Compound of Example 12	40.0 mg
Starch	109.0 mg
Magnesium stearate	1.0 mg
Total	<u>150.0 mg</u>

The active ingredient, cellulose, starch, and magnesium stearate are blended, passed through a No. 20 mesh U.S. sieve, and filled into hard gelatin capsules in 150 mg quantities.

Formulation Example 6

Suppositories, each containing 25 mg of active ingredient are made as follows:

5

Ingredient	Amount
Compound of Example 36	25 mg
Saturated fatty acid glycerides to	2,000 mg

10 The active ingredient is passed through a No. 60 mesh U.S. sieve and suspended in the saturated fatty acid glycerides previously melted using the minimum heat necessary. The mixture is then poured into a suppository mold of nominal 2.0 g capacity and allowed to cool.

15

Formulation Example 7

Suspensions, each containing 50 mg of medicament per 5.0 ml dose are made as follows:

20

Ingredient	Amount
Compound of Example 9	50.0 mg
Xanthan gum	4.0 mg
Sodium carboxymethyl cellulose (11%)	
Microcrystalline cellulose (89%)	50.0 mg
Sucrose	1.75 g
Sodium benzoate	10.0 mg
Flavor and Color	q.v.
Purified water to	5.0 ml

25

30 The medicament, sucrose and xanthan gum are blended, passed through a No. 10 mesh U.S. sieve, and then mixed with a previously made solution of the microcrystalline cellulose and sodium carboxymethyl cellulose in water. The sodium benzoate, flavor, and color are diluted with some of the water and added with stirring. Sufficient water is then added to produce the required volume.

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Formulation Example 8

Capsules, each containing 15 mg of medicament, are made as follows:

40

Ingredient	Quantity (mg/capsule)
Compound of Example 46	15.0 mg
Starch	407.0 mg
Magnesium stearate	3.0 mg
Total	425.0 mg

45

The active ingredient, cellulose, starch, and magnesium stearate are blended, passed through a No. 20 mesh U.S. sieve, and filled into hard gelatin capsules in 425 mg quantities.

50

Formulation Example 9

An intravenous formulation may be prepared as follows:

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Ingredient	Quantity
Compound of Example 1	250.0 mg
Isotonic saline	1000 ml

Formulation Example 10

A topical formulation may be prepared as follows:

Ingredient	Quantity
Compound of Example 1	1-10 g
Emulsifying Wax	30 g
Liquid Paraffin	20 g
White Soft Paraffin	to 100 g

The white soft paraffin is heated until molten. The liquid paraffin and emulsifying wax are incorporated and stirred until dissolved. The active ingredient is added and stirring is continued until dispersed. The mixture is then cooled until solid.

Formulation Example 11

Sublingual or buccal tablets, each containing 10 mg of active ingredient, may be prepared as follows:

Ingredient	Quantity Per Tablet
Compound of Example 21	10.0 mg
Glycerol	210.5 mg
Water	143.0 mg
Sodium Citrate	4.5 mg
Polyvinyl Alcohol	26.5 mg
Polyvinylpyrrolidone	15.5 mg
Total	<u>410.0 mg</u>

The glycerol, water, sodium citrate, polyvinyl alcohol, and polyvinylpyrrolidone are admixed together by continuous stirring and maintaining the temperature at about 90°C. When the polymers have gone into solution, the solution is cooled to about 50-55°C and the medicament is slowly admixed. The homogenous mixture is poured into forms made of an inert material to produce a drug-containing diffusion matrix having a thickness of about 2-4 mm. This diffusion matrix is then cut to form individual tablets having the appropriate size.

Another preferred formulation employed in the methods of the present invention employs transdermal delivery devices ("patches"). Such transdermal patches may be used to provide continuous or discontinuous infusion of the compounds of the present invention in controlled amounts. The construction and use of transdermal patches for the delivery of pharmaceutical agents is well known in the art. See, e.g., U.S. Patent 5,023,252, issued June 11, 1991, herein incorporated by reference. Such patches may be constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents.

Frequently, it will be desirable or necessary to introduce the pharmaceutical composition to the brain, either directly or indirectly. Direct techniques usually involve placement of a drug delivery catheter into the host's ventricular system to bypass the blood-brain barrier. One such implantable delivery system, used for the transport of biological factors to specific anatomical regions of the body, is described in U.S. Patent 5,011,472, issued April 30, 1991, which is herein incorporated by reference.

Indirect techniques, which are generally preferred, usually involve formulating the compositions to provide for drug latentiation by the conversion of hydrophilic drugs into lipid-soluble drugs or prodrugs. Latentiation is generally achieved through blocking of the hydroxy, carbonyl, sulfate, and primary amine groups present on the drug to render the drug more lipid soluble and amenable to transportation across the blood-brain barrier. Alternatively, the delivery of hydrophilic drugs may be enhanced by intra-arterial infusion of hypertonic solutions which can transiently open the blood-brain barrier.

The type of formulation employed for the administration of the compounds employed in the methods of the present invention may be dictated by the particular compounds employed, the type of pharmacokinetic profile desired from the route of administration and the compound(s), and the state of the patient.

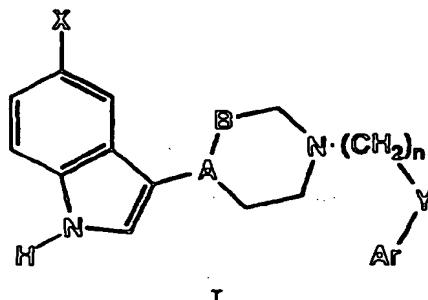
Claims

1. A compound of Formula I:

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10

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in which

A-B is -CH-CH₂- or -C=CH-;X is H, halo, C₁-C₄ alkoxy, C₁-C₄ alkylthio, C₁-C₄ alkyl, benzyloxy, hydroxy or carboxamido;

Y is O, S or a bond;

n is 1-4;

Ar is 1-naphthyl, 2-naphthyl, phenyl or phenyl monosubstituted with a substituent selected from the group consisting of halo, C₁-C₄ alkoxy, C₁-C₄ alkylthio, C₁-C₄ alkyl, benzyloxy, hydroxy or trifluoromethyl; and

pharmaceutically acceptable acid addition salts and hydrates thereof providing that:

- a) when Ar is phenyl and Y is a bond, X is other than halo; and
- b) when A-B is -C=CH-:

30

- i) X is not H or methoxy when Ar is phenyl and Y is a bond;
- ii) X is not H when Ar is 4-chlorophenyl, n is 1 and Y is a bond;
- iii) X is not hydroxy or benzyloxy when Ar is phenyl, n is 1 and Y is a bond.

35

2. A compound of Claim 1, in which A-B is -C=CH-.

3. A compound of Claim 1, in which A-B is -CH-CH₂-.

4. A compound of any of Claims 1-3 in which Y is a bond and n is 2-4.

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5. A compound of any of Claims 1-4, in which Ar is phenyl or phenyl monosubstituted with a substituent selected from the group consisting of halo, C₁-C₄ alkoxy, C₁-C₄ alkyl, or trifluoromethyl.

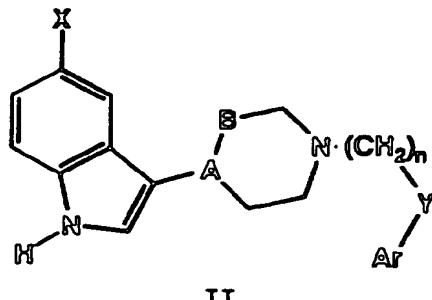
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6. A pharmaceutical formulation comprising as an active ingredient, a compound as claimed in any one of Claims 1-5, associated with one or more pharmaceutically acceptable carriers therefor.

7. A compound of Formula II:

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55



in which

15 A-B is -CH-CH₂- or -C=CH-;
X is H, halo, C₁-C₄ alkoxy, C₁-C₄ alkylthio, C₁-C₄ alkyl, benzyloxy, hydroxy or carboxamido;

Y is O, S or a bond;

n is 1-4;

20 Ar is 1-naphthyl, 2-naphthyl, phenyl or phenyl monosubstituted with a substituent selected from the group consisting of halo, C₁-C₄ alkoxy, C₁-C₄ alkylthio, C₁-C₄ alkyl, benzyloxy, hydroxy or trifluoromethyl; and

25 pharmaceutically acceptable acid addition salts and hydrates thereof, for use in the treatment of migraine and associated disorders.

25 8. A compound as claimed in Claim 7, for use in the inhibition of neuronal protein extravasation.

30 9. A compound as claimed in Claim 7, for use in activation of 5-HT_{1F} receptors in mammals.

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European Patent
Office

EUROPEAN SEARCH REPORT

Application Number
EP 95 30 8426

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
X	EP-A-0 303 506 (GLAXO GROUP LTD) 15 February 1989 * page 2, line 1 - line 16; claim 1; example 1 *	1-9	C07D401/04 A61K31/445
X,D	WO-A-93 14201 (SYNAPTIC PHARMACEUTICAL CORP) 22 July 1993 * the whole document * * especially pages 49, 54, 55 *	1-9	
X	EP-A-0 303 507 (GLAXO GROUP LTD) 15 February 1989 * intermediates 2, 3 *	7-9	
X	EP-A-0 003 199 (ROUSSEL UCLAF) 25 July 1979 * example 7 *	7-9	
X	US-A-3 947 578 (DERIBLE PIERRE HENRI ET AL) 30 March 1976 * example 4B *	7-9	TECHNICAL FIELDS SEARCHED (Int.Cl.6)
X	EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY CHIMICA THERAPEUTICA., vol. 22, no. 1, 1987 PARIS FR, pages 33-43, J. GUILLAUME ET AL. '(Tetrahydro-1,2,3,6 pyridinyl-4)-3 1H-indoles' * example 23 *	1-9	C07D
X	HELVETICA CHIMICA ACTA, vol. 51, no. 2, 1968 BASEL CH, pages 260-264, D. BECK ET AL. 'Synthese von 2- und 3-(1,2,3,6-Tetrahydropyridyl)-indolen' * examples IVC, IVD *	7-9	
		-/-	
The present search report has been drawn up for all claims			
Place of search	Date of completion of the search	Examiner	
THE HAGUE	5 March 1996	De Jong, B	
CATEGORY OF CITED DOCUMENTS			
X : particularly relevant if taken alone	T : theory or principle underlying the invention		
Y : particularly relevant if combined with another document of the same category	E : earlier patent document, but published on, or after the filing date		
A : technological background	D : document cited in the application		
O : non-written disclosure	L : document cited for other reasons		
F : intermediate document	& : member of the same patent family, corresponding document		



European Patent
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EUROPEAN SEARCH REPORT

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Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.)						
X	JOURNAL OF MEDICINAL CHEMISTRY, vol. 36, 1993 WASHINGTON US, pages 4006-4014, A. AGARWAL ET AL. 'Three dimensional quantitative structure-activity relationships of 5-HT receptor binding data for tetrahydropyridinylindole derivatives' * example 19 *	1-9							
X	CHEMICAL ABSTRACTS, vol. 84, no. 1, 5 January 1976 Columbus, Ohio, US; abstract no. 4794u. E. FRIDERICHSEN ET AL. 'Serotonin derivatives with cyclic side chains' compounds with RN=57477-30-2 and 57477-36-8 * abstract * & ARCH. PHARM., vol. 308, no. 9, 1975 pages 663-675, -----	7-9							
			TECHNICAL FIELDS SEARCHED (Int.Cl.)						
<p>The present search report has been drawn up for all claims</p> <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 33%;">Place of search</td> <td style="width: 33%;">Date of completion of the search</td> <td style="width: 34%;">Examiner</td> </tr> <tr> <td>THE HAGUE</td> <td>5 March 1996</td> <td>De Jong, B</td> </tr> </table>				Place of search	Date of completion of the search	Examiner	THE HAGUE	5 March 1996	De Jong, B
Place of search	Date of completion of the search	Examiner							
THE HAGUE	5 March 1996	De Jong, B							
<p>CATEGORY OF CITED DOCUMENTS</p> <p>X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document</p> <p>T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document</p>									